

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20201780>

Original Research Article

Role of serum anti mullerian hormone as a predictor for miscarriage

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Received: 27 January 2020

Revised: 21 February 2020

Accepted: 02 March 2020

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ABSTRACT

Background: Recurrent Miscarriage is defined as three or more failed clinical pregnancies at less than 20 weeks of gestation or fetal weight less than 500 grams that ends spontaneously. Ovarian reserve demonstrates reproductive potential and includes FSH, estradiol, inhibin B, and S. AMH levels. Women with very low AMH levels may have altered folliculogenesis that may influence early implantation to increase the risk of miscarriage. This study aimed to determine the serum AMH levels in patients with recurrent miscarriage and pregnancy outcomes in low (<1 ng/ml), normal (1-3.5 ng/ml) and high (>3.5 ng/ml) AMH groups and to evaluate the role of serum ovarian biomarkers in prediction of miscarriages.

Methods: This was a case-control study conducted over a time period of 1 year, on 120 women attending the antenatal clinic in department of obstetrics and gynecology, Swaroop Rani Nehru Hospital, Prayagraj. The patients were divided into two groups, Group 1 (n=80) included women with previous history of abortions and Group 2 (n=40) included women with no history of abortions. S. AMH levels were analyzed and compared in both the groups.

Results: In the present study, a significant negative correlation was seen between S. AMH and rate of miscarriages (p <0.05). Low AMH values were observed in patients with history of previous pregnancy loss.

Conclusions: Diminished ovarian reserve contributes to recurrent pregnancy loss and should be considered part of the work-up for RPL. AMH levels in recurrent miscarriage patients were lower than those in a normal population.

Keywords: Ovarian reserve, Pregnancy outcomes, Recurrent miscarriage

INTRODUCTION

Recurrent miscarriage is defined as three or more failed clinical pregnancies at less than 20 weeks of gestation or fetal weight less than 500 grams, that ends spontaneously prior the fetus can survive.¹ The World Health Organization (WHO) defines this un-survivable state as a fetus weighing 500 gm or less, which typically corresponds to a fetal age of 20-22 weeks. The estimated incidence of recurrent miscarriage is reported as between 1% and 5% of woman of reproductive age.¹

Known causes of miscarriage include chromosomal abnormalities, Infectious diseases, endocrinological

abnormalities, antiphospholipid antibodies, uterine anomalies.²⁻⁵ Several endocrinological abnormalities may include thyroid disease, uncontrolled diabetes and decreased ovarian reserve that may be implicated as etiologic factors for recurrent pregnancy loss. Approximately 50% of cases of recurrent miscarriages do not have a clearly defined etiology and are classified as unexplained.^{6,7} This high percentage suggests that current evaluation methods for women with recurrent miscarriages are insufficient.

AMH is a serum marker that reflects the number of follicles that have made transition from the primordial pool into the growing follicles pool that is not controlled

by gonadotropins, and would benefit both the patients and clinicians. It is a novel marker of ovarian reserve and a good predictor of oocyte quantity. Levels of AMH are stable within and between menstrual cycles. The association between advanced maternal age and miscarriage indicates that decreased ovarian reserve may have a possible connection with future pregnancy prognosis. The purpose of the present study is to evaluate and assess the predictive potential of serum ovarian reserve biomarkers, for pregnancy outcomes, in particular, miscarriage rates. Given that pregnancy loss is a common pregnancy outcome and AMH is a frequently utilized prognosticator of ovarian reserve, a potential association may have an important impact on reproductive aged women.⁸ Women with very low AMH levels may have altered folliculogenesis or steroidogenesis that may influence early implantation to increase the risk of miscarriage, regardless of chromosome status.

To determine the serum AMH levels in patients with recurrent miscarriage and pregnancy outcomes in low (<1 ng/ml), normal (1-3.5 ng/ml) and high (>3.5 ng/ml) AMH groups.

METHODS

This was a prospective observational case-control study. Among women attending the OPD clinic of Swaroop Rani Nehru hospital, Prayagraj. The duration of this study from June 2018 to June 2019.

Inclusion criteria

- Women who have definite history of spontaneous pregnancy losses/implantation failure, non-pregnant and pregnant
- Normal pregnant and non-pregnant women.

Exclusion criteria

- Women with documented
 - a. Uterine anomalies
 - b. Abnormal karyotype
 - c. Polycystic ovarian syndrome
 - d. Endometriosis.
- Women with
 - a. Chronic disease or
 - b. With chronic ongoing treatment
 - c. Thrombophilia
 - d. Documented endocrinopathies.

All women of 20-40 years of age after taking detailed history and thorough clinical examination were subjected to routine investigations. Serum Anti mullerian hormone was evaluated and analyzed. Women were followed up to see the conception rate and the outcome of pregnancy, in particular, miscarriage rate. The t-test for continuous variables and chi-square test for categorical variables were applied and correlation between these factors for

evaluation of miscarriage in patients with low ovarian reserve was seen.

Statistical analysis

For all statistical analysis p value <0.05 was considered as significant.

RESULTS

The total numbers of patients under study were divided into two major groups (Table 1). Patients with history of miscarriages were categorized as Group 1 which included 80 out of 120 women and patients with no history of miscarriages were categorized as Group 2 which included 40 out of 120 women.

Table 1: Distribution of cases under study (n = 120).

Group	Criteria	No. of cases
1	Cases-with history of miscarriages	80
2	Control-without history of miscarriages	40

Table 2: Distribution based on demographic variables (n=120).

Characteristics	No. of cases (n=120)	Percentage	
Age (years)	<30 years	88	73.33%
	≥30 years	32	26.66%
Literacy	Illiterate	39	32.50%
	Literate	81	67.50%
Residential area	Rural	65	54.17%
	Urban	55	45.83%
Age at marriage	<30 years	83	69.16%
	≥30 years	37	30.83%

In the study population, it was observed that 88 (73.33%) cases were of age group <30 years and 32 (26.66%) were above 30 years. Majority of the cases 81 (61.50%) were literate. More than half i.e. 65 (54.17%) cases belonged to rural area and 55 (45.83%) were from urban area. 83 (69.16%) cases were married before 30 years of age and 37 (30.83%) after 30 years of age (Table 2).

Serum AMH and its association with history of miscarriage

In Group 1, cases with low S. AMH levels were 47 (58.75%), 28 (35%) had normal AMH levels and 5 (6.25%) had high AMH. The serum AMH concentrations ranged from 0.19-6.11 in Group 1 with a mean value of 1.43 ng/ml. In Group 2, however, 7 (17.5%) patients had low AMH concentrations, 16 (37.5%) had normal AMH levels and 18 (45%) had high serum AMH values with a mean value of 3.49 ng/ml (Table 3). Hence, serum AMH concentrations were found to be associated with history

of previous pregnancy loss and the correlation was statistically significant ($p < 0.0001$).

Table 3: Comparison between 2 study groups according to serum AMH values.

Groups	S. AMH values (ng/ml)			Range	Mean±SD
	Low (<1 ng/ml)	Normal (1-3.5 ng/ml)	High (>3.5 ng/ml)		
1	47 (58.75%)	28 (35%)	5 (6.25%)	0.19-6.11	1.43±1.11
2	7 (17.5%)	16 (37.5%)	18 (45%)	0.49-6.61	3.49±1.81

p -value <0.0001.

Table 4: Number of patients conceived during the study in the two comparative groups.

Groups	No. of women conceived	Percentage
Group 1 (n=80)	34	42.5%
Group 2 (n=40)	26	65%

Comparison of rate of conception in the two groups

A total 34 (42.5%) out of the 80 women under study in Group 1, conceived spontaneously during the study and in Group 2, 26 (65%) were seen to have conceived (Table 4).

Analysis of the outcome of the pregnancies in the case and the control study groups

In Group 1, out of 34 women who conceived 21 (61.76%) were reported to have spontaneously aborted before 20 weeks and the mean S. AMH value was 1.58 ng/ml. 13 (38.23%) women were able to continue their pregnancy beyond 20 weeks, and mean S. AMH in them was 3.33 ng/ml (Table 5).

In Group 2, 26 women that conceived, 4 (15.38%) had spontaneous abortion with mean S. AMH of 3.74 and 22 (84.61%) continued their pregnancy beyond 20 weeks with mean S. AMH 5.24 (Table 6).

Table 5: Outcome of pregnancy in Group 1.

Outcome	Group 1 (n = 80)		S. AMH values (ng/ml)	
	No. of cases	Percentage	Range	Mean±SD
Aborted before 20 weeks	21	61.76 %	0.94-2.98	1.58±0.56
Pregnancy beyond 20 weeks	13	38.23%	1.88-6.11	3.33±1.29
Total	34	100%		

p value <0.0001.

Table 6: Outcome of pregnancy in Group 2.

Outcome	Group 2 (n = 40)		S. AMH values (ng/ml)	
	No. of cases	Percentage	Range	Mean±SD
Aborted before 20 weeks	4	15.38%	3.19-4.36	3.74±0.399
Pregnancy beyond 20 weeks	22	84.61%	3.2-6.61	5.24±1.02
Total	26	100%		

p value 0.0034.

Hence, a significant correlation was observed between S. AMH levels and the associated risk of spontaneous abortions ($p < 0.05$).

DISCUSSION

The present study was conducted on 120 women over a time period of one year. The patients were divided into two groups based on the history of previous miscarriages. 80 women with history of previous abortions were taken as the cases and 40 with no history of previous pregnancy losses were included as the control group (Table 1). The

main objective of the study was to assess the predictive potential of serum anti-mullerian hormone in pregnancy outcome, particularly miscarriage rates. The patients were evaluated for levels of anti-mullerian hormone, with the aim to identify its role as a risk factor for miscarriages and as a predictor of miscarriage. In the present study, a significant negative correlation was seen between serum anti-mullerian hormone and rate of miscarriages ($p < 0.05$).

Low AMH values were observed in patients with history of previous pregnancy loss. 47 (58.75%) women in

Group 1 had low AMH levels (<1 ng/ml) as compared to 7 (17.5%) in Group 2. Similar to this study, McCormack et al and Zamah et al observed in their study that low AMH levels are associated with recurrent miscarriages.^{9,10} Tarasconi et al, conducted a study that also supported the hypothesis that AMH is not only a biomarker of oocyte quantity but may be also related to oocyte reproductive potential.¹¹ Lyttle et al, observed that women with an AMH of ≤ 0.4 had over twice the risk of miscarriage.¹² In contrast to the present study, Zarek et al concluded that neither lower nor higher AMH were associated with pregnancy loss in women with a history of one or two prior pregnancy losses.⁸

It was observed that in Group 2, a higher number of women 34 out of 80 (65%) were seen to conceive during the study period as compared to 26 out of 40, (42.5%) in Group 1. Women with no history of miscarriage had higher conception rate. In an earlier, small pilot, Steiner et al, found that low AMH (<0.7 ng/ml) was associated with a 60% reduction in the day-specific probability of conception.¹³ In contrast, in a prospective study of 186 Danish women, Hagen et al, found that fecundability was not significantly reduced in women with low AMH (≤ 10 pmol/L, approximately ≤ 1.4 ng/ml) compared to women with normal AMH levels (HR 0.81, 95% CI 0.44-1.40).¹⁴

In the present study, it was seen that in Group 1, out of 34 women who conceived 21 (61.76%) had spontaneous abortion before 20 weeks and the mean S. AMH value was 1.58 ng/ml. In Group 2, 26 women that conceived, 4 (15.38%) had spontaneous abortion with mean S. AMH of 3.74. Hence, a significant correlation was observed between S.AMH levels and the associated risk of spontaneous abortion ($p < 0.05$) i.e. lower S. AMH values were observed in patients who aborted before 20 weeks. Similar to this study, Lyttle et al, concluded in a study that in women, with no known history of infertility and who conceived naturally, very low AMH (≤ 0.4 ng/ml) was associated with a higher risk of miscarriage.¹² Similarly, Atasaver et al showed that women with a history of miscarriage were three times as likely to have a low AMH (≤ 1 ng/ml) compared to age-matched, fertile controls.¹⁵ Prior studies by Szafarowska M et al and Gleicher N et al have suggested an increased risk of poor pregnancy outcome and increased risk of miscarriage among women with AMH values greater than 2.5 ng/ml.^{16,17} On the contrary, Zarek et al, and Pereira et al suggested women with a low AMH value (<1 ng/mL) did not have an increased risk of pregnancy loss.^{8,18}

CONCLUSION

Recurrent pregnancy loss (RPL) is a challenging disorder for both patients and clinicians. The present study was designed to evaluate the serum ovarian reserve biomarkers and thyroid hormone profile in the study groups and analyze its possible association with the risk of abortion during pregnancy.

The study concludes that diminished ovarian reserve may contribute in part to unexplained recurrent abortions. Therefore, diminished ovarian reserve may contribute to recurrent pregnancy loss and should be considered part of the work-up for RPL. In the present study, AMH levels in recurrent miscarriage patients were lower than those in a normal population. AMH levels may reflect quality, as well as quantity, of the remaining ovarian follicle pool.

Ovarian reserve testing is not currently routinely recommended in the work-up of recurrent pregnancy loss patients. However, findings of this study, along with the higher incidence of decreased ovarian reserve among recurrent pregnancy loss patients compared to the general population may provide a more compelling argument towards screening recurrent pregnancy loss patients for decreased ovarian reserve. RPL may be a considered a predictor of decreased ovarian reserve and obstetrician will be able to counsel patients more thoroughly with ovarian reserve tests, as part of their standard RPL work-up. Therefore, until further AMH outcome data are available, serum AMH when assayed in parallel to S.FSH have the greatest likelihood of detecting reduced ovarian reserve.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Singh UB, Srivastava Y, Dayal M, Jain S. Role of serum anti-mullerian hormone as a predictor for miscarriage. *Int J Reprod Contracept Obstet Gynecol* 2020;9:1919-23.