# Anti-Mullerian Hormone in Women with Recurrent Miscarriage

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## Abstract

In recent years, accumilated data indicate that "anti-mullerian hormonme (AMH)" reflects the number of follicles that have made the transition from the primordial pool into the growing follicle pool, and that is not controlled by gonadotropins. Ovarian reserve tests would be considered incomplete without AMH measurement. The study hypothesis aimed to answer a question: Is there a correlation between recurrent unexplained pregnancy loss and diminished ovarian reserve as reflected by serum level of AMH? sixty three non-pregnant female (34 females with history of unexplained three or more pregnancy losses within the last 5 years and 29 multiparas females without history of recurrent miscarriage as control). twenty six (41%) of the whole women included in the study had normal AMH while 22 (35%) of them had low and just 15 (24%) recorded high levels. Sixteen (44%) of women ≥35 year had low AMH compared to just 6 (22%) in women <35 year which was significantly different. Only 6 (17%) of those ≥35 year old had high AMH level. AMH level between women in cases and control showing that overall women with recurrent miscarriage had statistically significant lower AMH than in women in the control group (50%) and (17%) respectively. Although young women <35 years old in cases had lower AMH level (27%) compared to those in control (8%) but the difference was statistically not significant. In women ≥ 35 years old AMH levels were significantly lower in cases (68%) than in control (23.5%), even after adjusting for age .Four women (35.5%) in the control group had high AMH level while only one of women in cases group recorded such level.

**Key words**: Anti-Mullerian Hormone, Recurrent Miscarriage.

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## Introduction

"Anti-Mullerian hormone (AMH)" which is also termed as "Mullerian inhibiting substance (MIS)" a polypeptide, belongs to a super family of dimeric glycoproteins that are structurally similar to transforming growth factor beta , e.g. activins and inhibins[1]. AMH was initially thought to be produced solely in male embryos and secreted exclusively by immature Sertoli cells in the testis during sexual differentiation to promote involution of mullerian ducts[2]. In the nonattendance of AMH, Mullerian ducts grows into the uterus, fallopian tubes, and upper vagina in female embryos, despite of the absence of AMH in early female development, it is distinguished in the granulosa cells of the ovary towards 36 weeks of gestation. From birth till menopause, AMH is exclusively secreated by the follicles inside the ovary. Its level is lowest at birth and continues to be low throughout the prepubertal period, then increases at puberty and peaks at 25 years old and eventually decreases to undetectable levels at menopause[3].

Anti-Mullerian hormone is secreted by primary, secondary, preantral, and small antral follicles (4-6mm). Then after during follicular maturation its secretion reduces and follicles stop to secreate AMH as they have reached dominance consiquently, AMH is thought to be excreated by all follicles that are beyond the stage of the primordial follicle but have not yet reached the selection for dominance, these follicles represent the group that is independent on FSH, on the other hand it is not formed in the FSH-dependant antral follicles and also in atretic follicles therefore AMH serum level is constant during menstrual cycle and a small monthly fluctuations do occur[4]. However these changes are not regarded to be of clinical significance to recommend the measurement of AMH concentration at a precise phase of the menstrual cycle. Despite of that the specific role of AMH in human folliculogenesis stays to be clarified, it is generally thought to be a regulator of the recruitment and transformation from primordial follicles to growing follicles through paracrine and autocrine action preventing the depletion of all primordial follicle pool at once [5].

Recurrent spontaneous miscarriage (RSM) has been defined as three or more consecutive miscarriages, which have been proved by either ultrasound or histopathological study and it is suggested that some investigations should be performed after every miscarriage, with a carefull evaluation following three or more losses [6].A patient who has RSM without a previous viable pregnancy is defined as presenting with primary RSM on the other hand patients who present with an episode of RSM after one or more previous viable pregnancies are said to present with secondary RSM, and if the woman had at least three miscarriages that are not consecutive but are interspersed with pregnancies that had progressed to viability are termed tertiary RSM [7].

Recurrent pregnancy loss is a multi-factorial issue that may be related to endocrine dysfunction, autoimmune disorders, genetic abnormalities represented by inherited conditions, advanced maternal and paternal age, infectious causes, environmental toxins, and structural or congenital

uterine anomalies [8]. It is distressing to the affected families and the couple seeking partner hood, causing heartbreaking, frustration and [7] represent diagnostic, prognostic as well as therapeutic challenge for the treating physicians.

It is well appreciated that there is an age related reduction in a female's reproductive potential (9). This is partly because of a reduced chance to conceive, but greatly due to an increased risk of (very early) pregnancy loss. Women usually reach attends their peak reproductive potential before the age of 30 then undergo a slow decline in reproductive capacity till the age of 40, when the decline becomes more rapid(10). This process of woman's reproductive aging is related to a decline in both oocyte quantity, ultimately resulting in menopause, and oocyte quality. The main a known features of diminished quality is the creation of chromosomal abnormalities in the oocyte, causing aneuploidy in the conceptus, which has been accused as a reason for pregnancy loss in 35-75% of all cases(11).

The quality of female's oocytes cannot be evaluated clinically, but the quantity of the remaining follicle pool can be assessed by so called ovarian reserve tests (ORT). The antral follicular count (AFC) measured by ultrasound is believed to represent the quantitative aspect of ovarian aging (12) in addition other ORT screening tools have been used to estimate a female's reproductive potential(13), this generally includes measurement of early follicular phase FSH levels with or without an E2, the clomiphene citrate challenge test, AMH, and inhibin B (14).

Anti-Mullerian hormone measurement has been established to be an ideal marker for assessing the remaining oocyte pool and ovarian age being directly related to the number of antral follicles and is routinely carried out in anticipation of outcomes from ovarian stimulation, possibility of becoming pregnant after IVF and the onset of menopause [15,16,17,18,19].

In addition AMH seems to offer many advantages over other traditional markers of ovarian reserve. Studies suggested that AMH is constant during the menstrual cycle, moreover it is not affected by gonadotropin releasing hormone agonist, pregnancy, oral contraceptive pills, or by any of the feedback loops as well as being measured without inter-observer variations.

**Aim of the study:** To assess the possible relationship between AHM levels and unexplained recurrent miscarriage.

**Patients and methods:**

A cross-sectional study was conducted in Kirkuk governorate over aperiod of 49 months extending from the first of January 2013 till the first of February 2017 and included 63 non-pregnant female (34 females with history of unexplained three or more pregnancy losses within the last 5 years and 29 multiparas females without history of recurrent miscarriage as control) recruited from gynecological department of Azady Teaching Hospital and a private clinic.

Prior to blood sampling a special questionnaire was completed for each patient, that contains all required information, the purpose of the study was explained to each patient and written informed consent to participate in this study was obtained.

Complete history was obtained from patients and complete physical examination including body mass index (BMI), abdominal and pelvic examination, pelvic ultrasound examination to exclude uterine anomalies and any ovarian or pelvic pathology, serum anti-mullerian

hormone level was assayed at any day of menstrual cycle at patient's convenience. Other investigations were done for patients with recurrent miscarriage only including: complete blood picture, fasting blood sugar, HbA1C, TSH, prolactine, TORSCH screen, antiphospholipid antibodies(including: anticardiolipin antibodies, lupus anticoagulant IgG and IgM), screen for thrombophilia (including: anti-thrombin III, protein C, protein S and protein C resistance) and hysterosalpingography.

Cases were excluded from the study if they had:

1-Congenital anomalies of the uterus, intrauterine synechia, cervical incompetence and tubal occlusion.

2-Endometriosis and pelvic inflammatory disease.

3-Previous ovarian surgery, chemotherapy or radiotherapy treatment.

4-Ovarian dysfunction.(Polycystic ovarian syndrome)

5-Endocrine disease.(Diabetes, thyroid dysfunction and hyperprolactinemia)

6-Positive screen for immune or thrombophilic causes of recurrent miscarriage.

7-known genetic disease in either parent.

Anti-Mullerian Hormone (AMH) assay:

AMH level was estimated using ELISA kit imported from USA sera were extracted after centrifugation and kept at -20 degree centigrade till use. Prior to assessment all sera and the contents were thawed once and brought to room temperature and used for the assay. The procedure assay included the following steps: 100µl of diluent buffer was transferred in to microplates and then after 20 µl serial standards, positive and negative controls and for each serum has been added except the blank. AMH was clinically categorized and verified by data analysis into low (<1.25ng/ml), normal (1.25 to 4.0 ng/ml), and high (>4.0ng/ml).

**Statistical analysis**

Data was analyzed using "the statistical package for social sciences version 19 (SPSS Inc., Chicago, IL, USA)". A P-value of $\leq$ 0.05 was considered statistically significant.

**Results**:

After collection and categorization of the data from 63 women included in the study, statistical analysis was done and revealed the following :

The mean age for cases was 34.5 years; ranging between (23-43) years. 14 (41%) of patients were younger than 35 years and 20 (59%) of patients were older than 35 years, while the mean age for women in the control group was 33.8 years; ranging between (24-43) years. 13 (45%) of them were younger than 35 years and the remaining 16 women (55%) were older than 35 years and there was no statistically significant difference between the two applied groups regarding the age (P>0.05).

The mean body mass index (BMI) for cases was (22.3) which was not significantly different from that of control (21.6) (P>0.05) (Table 1).

The mean parity for cases (0.5) was significantly lower from that of controls (2.86) while the mean abortion rate for cases (2.7) (ranging between 3-5) was significantly higher than that in the control group (0.13). as shown in (Table 2)

Table 3 shows that 26 (41%) of the whole women included in the study had normal AMH while 22 (35%) of them had low and just 15 (24%) recorded high levels.

Sixteen (44%) of women ≥35 year had low AMH compared to just 6 (22%) in women <35 year which was significantly different. Only 6 (17%) of those ≥35 year old had high AMH level.

Table 4 compare AMH level between women in cases and control showing that overall women with recurrent miscarriage had statistically significant lower AMH than in women in the control group (50%) and (17%) respectively .

After adjusting for age, women in the cases with low AMH (<1.25ng/ml) had an increased risk of miscarriage in comparison to those with normal AMH levels "(1.25-4.0ng/ml) [Relative Risk (RR)=1.5, 95% Confidence intervals (CI) 0.7663 to 9.362]", whereas women with high AMH (>4.0ng/ml) had no significant increased risk of pregnancy loss compared to women with normal AMH levels "( 1.25-4.0) [(RR=0.8730 , 95% CI 0.5190 to 1.4686)]" .

Although young women <35 years old in cases had lower AMH level (27%) compared to those in control (8%) but the difference was statistically not significant. As shown in (table 5).

In women ≥ 35 years old AMH levels were significantly lower in cases (68%) than in control (23.5%), even after adjusting for age .

Four women (35.5%) in the control group had high AMH level while only one of women in cases group recorded such level. This is shown in table (6).

## Discussion:

Despite improvement in our understanding of reproductive physiology and embryonic development and improvement in diagnostic techniques, nearly half of the cases of recurrent miscarriage remain unexplained.

The current study was conducted to examine the potential contribution of diminished OR represented by low AMH in the etiology of unexplained RPM, since decreased oocyte quality with a, therefore, increased tendency toward embryonic chromosomal abnormalities which might account for these pregnancy losses has not been detectable in the course of standardized diagnostic evaluation for them[20,21].

Two acknowledged predictive factors for miscarriage namely female age & BMI were identified in our study and were comparable between the two groups as shown in table (1).

Forty-seven percent of women included in this study were young (<35 years) while 57% were ≥35 years.Women ≥35 years had significantly lower AMH level compared to younger women <35 years (44% vs 22%) as shown in table 3

With increasing age there is a decline in the number of primordial follicle, since AMH is expressed by growing follicles up to selection, this will be acompanied by concomitant decrease in serum concentration of AMH. This agrees with the results of other studies[22,23] observing that AMH serum concentration decreases steadily in a manner highly correlated with advancing age.

In addition an inverse correlation between BMI and AMH levels was found in other studies [17,22,23]. The using of a matched groups regarding these two factors (age and BMI) for comparison in this study minimizes the possibility that a relation between miscarriage and AMH was misinterpreted.

Before the introduction of AMH for OR the older tests for OR namely basal FSH has been correlated with oocyte quality and IVF outcome [24]. and numerous investigators have studied the possible link between diminished OR and fetal aneuploidy. The result of these studies are mixed, but many of them suggest a relation between raised basal FSH level and fetal aneuploidy that might not be expected by woman's age alone[24,25,26]. While others failed to find a link between diminished OR and

miscarriage and they explained this by that ORTs are actually related to the number of oocyte remained and that their quality is unrelated to their quantity [11,21,27].

Actually when the association between oocytes quality and quantity is subtle, erroneous estimation of quantitative OR might obscure this association and the cause that ORTs did not predict miscarriage in these studies could be that these tests do not correctly reflect oocytes quantity. Another explanation may be that the association between oocyte quality and quantity does exist, but only at the extremes of reproductive age, when OR is markedly diminished[11]. Because raised FSH level is often a late sign of reduced OR, it is suggested that an earlier, more sensitive marker of reduced OR might be more obviously associated with fetal aneuploidy.

It is widely accepted now that the decline in AMH levels in serum is the initial indicator of a diminished follicular reserve of the ovaries and the predictive value of AMH exceeds the performance of ovarian reserve testing with age, FSH, inhibin B and estradiol[28,29].

In our study patients with RM had significantly lower AMH compared to those in the control group (50% and 17%) respectively as shown in table (4). This is in agreement with the results of study done by Sophie et al[20] that compared women with explained & idiopathic recurrent miscarriage finding that lower basal estradiol & AMH levels predicts the presence of IRM, whereas basal FSH & LH as well as age didn't, others studies[30,31] also found the same results.

This finding may be explained by the fact that reduction in serum AMH level caused by ovarian aging reflects a reduction in the size of primordial follicle pool as well as an increasing rate of per-follicle granulosa cell apoptosis, which would be blamed to reduce the per-follicle excreation of AMH and diminished oocyte quality associated with an increase in fetal aneuploidy and pregnancy losses [32]. This is online with the results of McCormack *et al* [33]in a study using same age groups finding that patient with RM have significantly lower AMH levels than those in control group.

On the other hand the result of other studies did not prove any significant difference between the study and control groups regarding the level of AMH[25,27,34,35]. The discordance between this study and the others may be explained by the difference in the study design and inclusion of patient who were treated in infertility clinic [34] or from IVF centers or of different races [35] or the use of different assay method for AMH measurement [25].

In this study women ≥35 year old had significantly lower AMH compared to controls in the same age group (p value <0.05) as shown in table (6) It has been hypothesized that the germ cells produced initially during fetal developement are the least prone to non-disjunction, these oocytes are selected for ovulation sooner, leaving the oocytes of diminished quality with altered meiotic spindle formation for later years [11,36,37], since decline in oocyte quantity with age is associated with deterioration of quality; it is reasonable to speculate that decline in the ovarian reserve that is regareded to be a reflection of advanced ovarian aging could impact a woman's risk for pregnancy loss due to aneuploidy [25].

In the current study although younger women <35 years old with RM had lower AMH compared to age-matched control group but the difference was not statistically significant (p value >0.05) as shown in table (5). This is online with the

findings of Catherine et al[33] that showed lower AMH level in patients with RM than in those of normal population in both above and below 35 years old women.

In some female the ovarian aging process does not all the time correlate with chronologic age. Therefore ovaries may be depleted of their oocytes at a rate faster than that which would be expected by age alone in these female who undergo accelerated ovarian aging it is reasonable that oocyte quality is also exhausted [38].

Leclercq et al in a similar study but with a different age groups find that women older than 25 years old with RUM showed significantly lower AMH than in control group, conversely younger women <25 years old showed significantly lower AMH level in controls than in cases. This discrepancy in the findings with that of our study may be related to the use of obviously younger patients than in ours.

As a conclusion of current study and within the limit of the cases evaluated, low AMH correlates with RPL especially after the age of 35 years and AMH measurement might be more cost effective if reserved for subjects in this age group, on the other hand if we did so we would missed 27% of the patients who had low levels and were <35 years old. It consequently appears to be prudent to test for diminished OR for all patients who present for assessment. Women with low AMH who are able to achieve pregnancy may require counseling for increased risk of subsequent pregnancy loss and serum AMH levels may be added to routine workup for RPL.

Table (1): The demographic characteristics of the two studied groups according to the age and BMI.

| Demographic Characteristics | | Cases | | Control | | P value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| Age | <35 | 14 | 41 | 13 | 45 | 0.6 |
| | ≥35 | 20 | 59 | 16 | 55 | |
| BMI ($kg/m^2$)(Mean±SD) | | 22.3±3.86 | | 21.6±2.86 | | 0.2 |

Table (2): Comparison between the two studied groups according to parity and abortion

| Studied Women / Obstetrical History | Cases | | | | Total | Control | | | | Total | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <35 | | ≥35 | | | <35 | | ≥35 | | | |
| | No. | % | No. | % | | No. | % | No | % | | |
| **Parity** | | | | | | | | | | | |
| 0 | 10 | 46 | 12 | 54 | 22 | 0 | 0 | 0 | 0 | 0 | |
| 1 | 3 | 43 | 4 | 57 | 7 | 0 | 0 | 0 | 0 | 0 | 0.00001 |
| 2 | 0 | 0 | 2 | 100 | 2 | 6 | 60 | 4 | 40 | 10 | |
| 3 | 1 | 33 | 2 | 67 | 3 | 5 | 42 | 7 | 58 | 12 | |
| ≥4 | 0 | 0 | 0 | 0 | 0 | 2 | 28 | 5 | 72 | 7 | |
| Mean±SD | 0.5±0.9 | | | | 34 | 2.86±0.7 | | | | 29 | |
| **Abortion** | | | | | | | | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | 13 | 45 | 16 | 55 | 29 | |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00001 |
| 3 | 7 | 41 | 10 | 59 | 17 | 0 | 0 | 0 | 0 | 0 | |
| 4 | 6 | 55 | 5 | 45 | 11 | 0 | 0 | 0 | 0 | 0 | |
| ≥5 | 1 | 17 | 5 | 83 | 6 | 0 | 0 | 0 | 0 | 0 | |
| Mean±SD | 2.7±0.7 | | | | 34 | 0.13±0.3 | | | | 29 | |

Table (3): Distribution of AMH according to age groups for all women in the study.

| Age / AMH | Studied Women | | Low | | NR | | High | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| <35 year | 27 | 43 | 6 | *22 | 12 | 44 | 9 | *34 |
| ≥35 year | 36 | 57 | 16 | *44 | 14 | 39 | 6 | *17 |
| Total | 63 | 100 | 22 | 35 | 26 | 41 | 15 | 24 |

*P<0.05

Table (4): Comparison between the two studied groups according to AMH.

| AMH level / Studied Women | Cases | | Control | | P value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Low | 17 | 50 | 5 | 17 | |
| Normal (Satisfactory) | 12 | 35 | 14 | 48 | <0.05 |
| High (Potential fertility) | 5 | 15 | 10 | 35 | |
| Total | 34 | 100 | 29 | 100 | |

Table (5): Analysis of women subpopulation aging <35 year.

| Studied Women / AMH level | Cases | | Control | | P value |
|---|---|---|---|---|---|
| | <35 | | <35 | | |
| | No. | % | No. | % | |
| Low | 4 | 27 | 1 | 8 | >0.05 |
| Normal (Satisfactory) | 7 | 46 | 7 | 58 | |
| High (Potential fertility) | 4 | 27 | 4 | 34 | |

Table (6): Analysis of women subpopulation aging ≥35 year.

| Studied Women / AMH level | Cases | | Control | | P value |
|---|---|---|---|---|---|
| | ≥35 | | ≥35 | | |
| | No. | % | No. | % | |
| Low | 13 | 68 | 4 | 23.5 | <0.05 |
| Normal (Satisfactory) | 5 | 26 | 7 | 41 | |
| High (Potential fertility) | 1 | 6 | 6 | 35.5 | |

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