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Anti-müllerian hormone and pregnancy loss from the EAGeR trial

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Abstract

Objective—To evaluate if anti-Müllerian hormone (AMH) is associated with pregnancy loss.

Design—A prospective cohort study within a block-randomized, double-blind, placebo-controlled trial of low dose aspirin.

Setting—Four U.S.A. clinical sites (2006-2012).

Patients—Women (n=1228) were aged 18-40 years with a history of one to two pregnancy losses and were actively attempting pregnancy without fertility treatment.

Interventions—None.

Main Outcome Measures—Pregnancy loss.

Results—Relative risks (and 95% CI) of hCG detected and clinical pregnancy loss were assessed using log binomial models with robust variance and inverse probability weights adjusted for age,

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Capsule: Lower and higher AMH levels are not associated with hCG detected or clinical pregnancy loss in unassisted conceptions in women with a history of pregnancy loss.

race, BMI, income, trial treatment assignment, parity, number of previous losses, and time since most recent loss. AMH levels were defined as: low (<1.00 ng/mL) (n=124), normal (referent; 1.00 to 3.5 ng/mL) (n=595), and high (>3.5 ng/mL) (n=483). Of the 1202 women with baseline AMH data, 19 (17.3%) women with a low AMH experienced a clinical loss, compared to 61 (11.4%) with normal AMH and 50 (11.8%) with a high AMH level. Low or high AMH levels relative to normal AMH (referent) were not associated with clinical loss (Low AMH: RR, 1.13, 95% CI 0.74, 1.72; High AMH: RR 1.13, 95% CI 0.82, 1.56). Results for hCG detected pregnancy loss mirrored those of clinical loss.

Conclusions—AMH values were not associated with hCG detected or clinical pregnancy loss in unassisted conceptions in women with a history of one to two prior losses. Our data do not support routine AMH testing for prediction of pregnancy loss.

Keywords

anti-Müllerian hormone; pregnancy loss; miscarriage; spontaneous abortion; aneuploidy

INTRODUCTION

Pregnancy loss is common, affecting up to 15% of all clinically confirmed pregnancies (1, 2), and is associated with increasing maternal age (3). After experiencing a loss, couples desire information about future risk of subsequent pregnancy loss. Whereas current practices of ultrasonography are extensively utilized to predict real-time pregnancy viability (4), less is known about preconception biomarkers to predict the risk of loss in a future pregnancy.

AMH is a dimeric glycoprotein from the transforming growth factor β family (5, 6) and is well established as a predictor of ovarian reserve (7-10). It has been evaluated as a marker of ovarian aging (11, 12), with a decline in AMH linked to increasing maternal age (12). Although AMH has been postulated to be useful for predicting pregnancy loss (13) and aneuploidy risk (14-18), its association with pregnancy loss is unclear. Some investigators report a significant link between AMH and pregnancy loss (13), while others report no association (19, 20). Furthermore, the relationship between AMH and pregnancy loss has never been evaluated in unassisted conceptions in a cohort with well characterized reproductive history. Thus, the objective of this analysis was to investigate the association between preconception AMH and pregnancy loss and aneuploidy in fecund women with a history of pregnancy loss. 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.

METHODS

Study Design and Population

This is a secondary analysis of a prospective cohort of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, a multi-center, double-blind, block-randomized, placebo-controlled trial evaluating the effect of low dose aspirin (LDA) on live birth in 1228 women with a history of one to two previous losses. The EAGeR study was conducted from 2006–2012 at four U.S. clinical centers; the design and methods have been previously described

(21). Women in this cohort were attempting pregnancy, aged 18–40 years, with regular menstrual cycles of 21–42 days in length and a history of one to two prior pregnancy losses and no history of infertility, pelvic inflammatory disease, tubal occlusion, endometriosis, anovulation, uterine abnormality, or polycystic ovarian syndrome. Fertility monitors were used to assist with timing intercourse and scheduling clinic visits (Clearblue Easy Fertility Monitor; Inverness Medical). Eligible participants reported their reproductive history which was classified by 1) number of prior live births (none or any), 2) number of prior pregnancy losses (1 or 2), and 3) time since most recent loss (≤ 1 or >1 year). Written informed consent was provided by all participants. Institutional Review Board authorization was obtained for the data coordinating center and at all clinical centers. Patient safety was optimized by the Data Safety and Monitoring Board (DSMB) and the trial was registered with ClinicalTrials.gov, number NCT00467363.

AMH Assessment

Preconception AMH concentrations were measured in serum samples collected prior to conception at the randomization visit scheduled to coincide with day 2–4 of the menstrual cycle. AMH was analyzed in 2014 on samples collected 2007-2012 and promptly stored at −80 °C, using the GEN II ELISA™ assay protocol with correction for complement interference (Beckman Coulter) (22). AMH levels were available for 1202 of the 1228 (97.9%) women in the cohort. All machine observed concentrations were used without substitution of concentration below the limits of detection (0.006 ng/ml) to avoid bias (23). The interassay laboratory coefficients of variation were 6.2 and 6.6% at mean concentrations of 8.9 and 3.1 ng/mL, respectively, for lyophilized manufacturer's controls and 6.3% for an in-house pooled serum control. In order to maximize measurement precision of AMH, we evaluated for out-of-range values for manufacturer-provided control samples utilizing a pooled standard curve and confirmed that sample recalibration was not required (24).

Outcome Measures

hCG detected pregnancy and detection of hCG loss—Detection of an hCG pregnancy was defined as a positive result on a urine pregnancy test sensitive to hCG level of 25 mIU/ml (Quidel Quickvue, Quidel Corporation, San Diego, CA). These urine hCG pregnancy tests were conducted at home or at the clinic if a participant reported a missed menses. In addition to the urine hCG tests, free beta hCG was measured in daily first-morning urine collected at home from the last 10 days of each woman's first and second menstrual cycle of study participation, and on spot urine samples collected at study visits timed to coincide with day 2-4 of the expected next menstrual cycle to enable a more sensitive detection of very early pregnancy. Two laboratory assays for free beta hCG (initial test: catalogue no. RIS0011R, BioVendor, Asheville, NC, USA; confirmatory test: catalogue no. 4221-16, Diagnostic Automation Inc., Calabasas, CA, USA) were sequentially utilized to identify 21 additional pregnancies that were verified as very early positive tests for hCG detected pregnancy. An hCG detected loss was defined as the detection of an hCG pregnancy followed by the absence of signs of clinical pregnancy and ensuing menses.

Clinical pregnancy and detection of clinical loss—Clinically confirmed pregnancy was defined as a pregnancy identified by early ultrasound at approximately 6-7 weeks of

gestation. Clinically confirmed pregnancy losses included 1) pre-embryonic loss 2) embryonic loss 3) fetal loss 4) stillbirth 5) ectopic and 6) pregnancy of unknown location (25) (See Supplement for definitions).

Chromosomal Analysis for Aneuploidy of Pregnancy Losses—Genetic testing was conducted at two of the four centers participating in the study and was initiated on 82 of the 133 clinical pregnancy losses (26). Participants were given labeled sterile specimen containers and clean gloves when they had a positive pregnancy test or at their ultrasound, and instructed in the event of a pregnancy loss to place any passed tissue in a specimen container, keep it chilled and contact the research nurse as soon as possible. Tissue was also obtained from several participants via a dilatation and curettage procedure. Determinate results were obtained in 55 (41%) of pregnancy losses. Samples were sent to a cytogenetic laboratory for karyotyping. In some cases, chromosomal microarray was performed if karyotype failed. Results were classified as normal, abnormal, or unable to determine. Of note, only aneuploidy by microarray was considered abnormal; copy number variants were considered non-informative

Statistical analysis

At present, international standards of AMH thresholds do not exist for the general, fertile population. Analysis of AMH levels using the continuous data, demonstrated a potential non-linear (U-shaped) relationship between AMH and pregnancy loss, suggesting that conventional linear regression would not be appropriate. We performed extensive, careful review of available data in order to define the AMH categories utilized. Several sensitivity analyses were performed, including tertile analyses, to determine the most appropriate cut-points of AMH, all which demonstrated similar null findings. Our choice of cut-points presented here was intended to best reflect cut-points in current clinical use which reflect a reasonable distribution of women across the groups. AMH levels for this analysis were categorized utilizing clinical thresholds based on data from infertile women (27-29): low (<1.00 ng/mL), normal (1.00 to 3.5 ng/mL), and high (>3.5 ng/mL). Analysis of variance (ANOVA), Chi-Square test or Fisher's exact test were used, as appropriate, to determine differences across low, normal, and high AMH categories for demographic and reproductive history characteristics.

Log binomial models with robust variance were utilized to estimate relative risks (RR with 95% CI) of two outcomes, first, hCG detected pregnancy loss and second, clinically confirmed pregnancy loss associated with low and high AMH levels compared to normal AMH (reference group). In order to correctly estimate the effect of AMH on pregnancy loss, inverse probability weights (30) were implemented to control for potential bias introduced by restricting the analysis to only women with an hCG detected pregnancy. Given that little is known about the impact of prior pregnancy loss and parity history on the relationship between AMH and pregnancy loss, analyses were repeated among: 1) women with versus without a prior live birth; 2) women with 1 versus 2 prior pregnancy losses; and, 3) women with the most recent pregnancy loss within the prior year versus ≥ 1 year prior. The choice of covariates to include in fully adjusted models was determined by directed acyclic graphs and statistical testing for confounding identification. Models adjusted for age only are

presented as well as models adjusted for age, race, BMI, income, and LDA treatment assignment, with additional adjustment for parity, number of previous losses, and time since most recent loss for analyses not stratified by these same characteristics. In addition, we conducted an exploratory evaluation of AMH and aneuploidy of pregnancy loss.

Information was missing in some cases for AMH (n=26), BMI (n=20), education (n=1), gestational age of most recent loss (n=161), time from last loss to randomization (n=20), and chromosomal status of clinical pregnancy loss (n=75). Multiple imputation was performed for missing exposure, covariate, and outcome data, assuming data were missing at random (31). For analyses evaluating aneuploidy, inverse probability weighting was also utilized. Analyses were conducted using SAS software (version 9.4; SAS Institute, Inc.).

RESULTS

Participants were predominantly white (96.8%), married (94.9%), and high school educated or above (89.8%), with a mean body mass index of 25.5 (6.1 kg/m^2) and age 28.7 (±4.6) years. Mean age was highest in the low AMH group and lowest in the high AMH group ($p<0.001$). In parallel with age distribution across groups, women within the lower AMH levels also had higher income ($p<0.001$, data not shown), and a marginally greater proportion with history of prior births ($p=0.07$). Race, LDA treatment, number of previous pregnancy losses, gestational age of last loss, and time from last loss to randomization were similar across AMH groups.

There were a total of 185 pregnancy losses in women with AMH data available (n=55 hCG detected losses and n=130 clinical losses). The AMH range of participants was 0.07 ng/ml to 22.1 ng/ml. Characteristics of participants achieving a clinical pregnancy (n=708) are shown in **Table 1**. Characteristics of participants achieving an hCG detected pregnancy with a measured AMH level (n=769) are shown in **Supplemental Table 1**. Of the 708 participants who achieved a clinical pregnancy, the majority of the participants demonstrated a normal (n=346, 48.9%) or high (n=289, 40.8%), compared to 73 (10.3%) women who demonstrated a low AMH.

There were no significant differences in the percentage of women experiencing a clinical loss by AMH category, with 19 (15.3%) women with low AMH experiencing a clinical loss, compared to 61 (10.3%) with normal AMH and 50 (10.4%) with a high AMH level. Similarly, there were no significant differences in hCG detected losses by AMH level (**Table 2)**. Low and high AMH compared to normal AMH was not significantly associated with hCG detected or clinical loss in unadjusted analysis, nor adjusted models. In analyses stratified by: 1) number of prior live births; 2) number of prior pregnancy losses; and, 3) time since most recent loss, there was no significant association between low or high AMH and an hCG detected or clinical loss.

Determinate karyotype or microarray results were obtained in 55 pregnancy losses and classified as normal (n=26, euploid), or abnormal (n=29, aneuploid) with the majority of aneuploid cases diagnosed as an autosomal trisomy (n=15). There were no significant associations of low or high AMH with an increased risk of aneuploidy of clinically

confirmed pregnancy losses with a determinate karyotype in unadjusted analysis, or adjusted models (**Table 3**).

DISCUSSION

To our knowledge, this is the first prospective study to evaluate the relationship between preconception AMH level and pregnancy loss in unassisted conceptions of a large cohort of women with previous loss and confirmed prior fecundity. AMH was not associated with hCG detected or clinical pregnancy loss and further examination according to reproductive history characteristics did not identify significant associations, indicating these reproductive characteristics did not modify the potential relationship of AMH with pregnancy loss.

These findings clarify the relationship between AMH and pregnancy loss, following prior studies in other populations which have shown inconsistent results. One group reported a significant association with pregnancy loss with a low AMH (≤ 1.12 ng/ml) in women undergoing assisted reproduction (n=54, mean age 36.6 years) (13), whereas other studies found no association between AMH and pregnancy loss (19, 20). These prior findings may be further complicated by the inclusion of women with known diseases affecting pregnancy loss, such as polycystic ovarian syndrome (PCOS) (19, 20), which was a self-reported exclusion criterion in our cohort. Women with PCOS generally have higher AMH levels (29) but may have a higher risk of pregnancy loss (32, 33). Our data indicate that outside the context of PCOS and/or infertility, which complicates interpretation of prior studies, AMH is not independently associated with risk of pregnancy loss.

Given that AMH is an established marker of ovarian reserve, some postulate that AMH is also a marker of oocyte competence (34, 35), thereby having implications for pregnancy success or loss. However, the absence of an association between AMH and pregnancy loss identified here does not support that AMH is a preconception marker of oocyte competence translating to pregnancy loss risk. As such, age (along with number and type of prior losses) remains one of the most informative factors available for preconception counseling on future risk of losses in women with a history of pregnancy loss. Indeed, female age is known to predict oocyte competence, as demonstrated by the increase in meiotic disjunction and aneuploidy in pregnancies of older women (36). Although previous studies have reported an association of AMH and aneuploidy (14, 16-18), our exploratory analyses show no association. This analysis not only included karyotype, but also chromosomal microarray that allows for additional differentiation of genetic abnormalities in early losses (26). Lastly, we were missing karyotype information on approximately one third of the clinically recognized pregnancy losses, which may limit our power to detect effects. Nonetheless, missing and indeterminate karyotypes in our study were accounted for in rigorous statistical analyses by inverse probability weights and multiple imputation.

Our study has many strengths, including preconception measurement of AMH in a large cohort of over 1200 women, early documentation of pregnancy both by urine and 6-7 weeks' gestation ultrasonography, careful monitoring of pregnancy outcomes, and prospectively monitored aneuploidy of the clinical losses. Furthermore, our study provides an assurance of fertility in this study sample of women as the participating women all had prior pregnancies

per the eligibility requirement of having had a prior pregnancy loss. By collecting daily first morning urine in the first and second cycle of women attempting pregnancy, we were able to detect very early pregnancies and losses. One limitation of this study is the overall generalizability of the findings to a broader fertile population, as this study only included women with a history of pregnancy loss. However, pregnancy loss is a common event, occurring in an estimated 30% of conceptions (1, 37), suggesting that this study population is relevant to a large proportion of reproductive aged women.

In conclusion, neither lower nor higher AMH were associated with pregnancy loss in women with a history of one or two prior pregnancy losses. Thus, AMH likely does not purport clinical utility for preconception counseling of future pregnancy loss risk in women with a history of one or two pregnancy losses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics of participants of the EAGeR cohort achieving a clinically confirmed pregnancy

Characteristics	Total	Low AMH <1.0 ng/ml	Normal AMH 1.0-3.5 ng/ml	High AMH >3.5 ng/ml	P Value[a]
n (%)	708	73 (10.3)	346 (48.9)	289 (40.8)	
Age, y	28.7 ± 4.6	32.6 ± 4.8	29.0 ± 4.6	27.3 ± 3.9	<0.001
BMI, kg/m^2	25.5 ± 6.1	25.6 ± 6.4	25.6 ± 6.2	25.2 ± 5.8	0.70
Race					0.78
White	685 (96.8)	72 (98.6)	334 (96.5)	279 (96.5)	
Non-White	23 (3.2)	1(1 .4)	12 (3.5)	10(3.5)	
Marital status					0.78
Living with partner	25 (3.5)	4 (5.5)	10 (2.9)	11 (3.8)	
Married	672(94.9)	69 (93.2)	330 (95.4)	274 (94.8)	
Other	11 (1.6)	1(1.4)	6 (1.7)	4 (1.4)	
> High School Education	636 (89.8)	62(84.9)	317 (91.6)	257 (88.9)	0.18
Treatment					
Placebo	342 (48.3)	30 (41.1)	174 (50.3)	138 (47.8)	0.35
Low Dose Aspirin	366 (51.7)	43 (58.9)	172 (49.7)	151 (52.2)	
Parity					0.05
Nulliparous	295 (41.7)	30 (41.1)	129 (37.3)	136 (47.1)	
Parous (1 or 2 prior live births)	413 (58.3)	43 (58.9)	217 (62.7)	153 (52.9)	
Number of previous pregnancy losses					0.57
1	470 (66.4)	50 (68.5)	223 (64.5)	197 (68.2)	
2	238 (33.6)	23 (31.5)	123 (35.5)	92 (31.8)	
Gestational age of most recent loss, wks	9.3 ± 4.7	9.7 ± 5.1	9.3 ± 4.6	9.2 ± 4.8	0.74
Time from last loss to randomization					0.06
≤ 4 months	419 (60.4)	50 (69.4)	203 (60.1)	166 (58.5)	
5-8 months	126 (18.2)	10 (13.9)	51 (15.1)	65 (22.9)	
9-12 months	48 (6.9)	5 (6.9)	26 (7.7)	17 (6)	
>12 months	101 (14.6)	7 (9.7)	58 (17.2)	36 (12.7)	

[a]P -values based on Analysis of Variance (ANOVA) test for continuous variables, and χ^2 test (or Fisher's exact test when cell count <5) for categorical variables. Information was missing for BMI (n=9), gestational age of most recent loss (n=94), time from last loss to randomization (n=14).

Table 2

AMH and hCG detected or clinical loss among women with hCG or clinical or detected pregnancy stratified by reproductive history

	hCG detected Loss			Clinical Loss		
	Low AMH <1.0 ng/ml	**Normal AMH 1.0-3.5 ng/ml**	**High AMH >3.5 ng/ml**	**Low AMH <1.0 ng/ml**	**Normal AMH 1.0-3.5 ng/ml**	**High AMH >3.5 ng/ml**
Overall, Experienced loss-no (%)	5 (4.0)	27 (4.5)	23 (4.8)	19 (15.3)	61 (10.3)	50 (10.4)
RR, Unadj.	0.95 (0.47,1.94)	Ref	0.95 (0.59,1.53)	1.32 (0.87,2.01)	Ref	1.03 (0.76,1.4)
RR, *Adj. Model 1	0.89 (0.42,1.86)	Ref	0.99 (0.61,1.61)	1.17 (0.77,1.79)	Ref	1.1 (0.80,1.49)
RR, †Adj. Model 2	0.90 (0.42,1.91)	Ref	0.99 (0.55,1.79)	1.13 (0.74,1.72)	Ref	1.13 (0.82,1.56)
History of no previous live births (n=561), Experienced a loss - no. (%)	3 (6.1)	12 (5.4)	13 (6.1)	5 (10.2)	26 (11.7)	28 (13.2)
RR, Unadj.	0.59 (0.19,1.79)	Ref	0.99 (0.55,1.79)	1.29 (0.76,2.18)	Ref	1.02 (0.69,1.5)
RR, *Adj. Model 1	0.48 (0.16,1.49)	Ref	1.08 (0.60,1.96)	1.13 (0.66,1.93)	Ref	1.06 (0.72,1.57)
RR, ††Adj. Model 2	0.47 (0.15,1.47)	Ref	1.09 (0.61,1.97)	1.14 (0.66,1.96)	Ref	1.09 (0.73,1.61)
History of live birth (n=641), Experienced a loss - no. (%)	2 (3.3)	15 (4.9)	10 (4.7)	14 (23.3)	35 (11.3)	22 (10.4)
RR, Unadj.	1.59 (0.62,4.08)	Ref	1.09 (0.6,1.98)	1.4 (0.73,2.7)	Ref	1.09 (0.66,1.77)
RR, *Adj. Model 1	1.72 (0.66,4.48)	Ref	0.81 (0.34,1.96)	1.27 (0.65,2.5)	Ref	1.17 (0.7,1.97)
RR, ††Adj. Model 2	0.94 (0.35,2.47)	Ref	1.2 (0.64,2.22)	1.47 (0.75,2.87)	Ref	1.16 (0.69,1.94)
History of one previous loss (n=804), Experienced a loss - no. (%)	2 (2.7)	16 (5.0)	16 (5.6)	12 (16.0)	37 (10.5)	31 (10.8)
RR, Unadj.	1.19 (0.77,1.85)	Ref	0.90 (0.62,1.29)	0.83 (0.38,1.82)	Ref	1.06 (0.70,1.62)
RR, *Adj. Model 1	1.1 (0.46,2.65)	Ref	0.87 (0.46,1.65)	0.79 (0.35,177)	Ref	1.09 (0.71,1.66)
RR, ††Adj. Model 2	0.89 (0.35,2.24)	Ref	0.97 (0.5,1.88)	0.80 (0.36,1.81)	Ref	1.13 (0.71,1.79)
History of two previous losses (n=398), Experienced a loss - no. (%)	3 (8.8)	11 (6.1)	7 (5.2)	7 (20.6)	24 (13.3)	19 (14.0)
RR, Unadj.	0.89 (0.35,2.28)	Ref	0.96 (0.49,1.88)	1.83 (1.12,2.99)	Ref	0.90 (0.58,1.38)
RR *Adj. Model 1	0.73 (0.21,2.59)	Ref	0.99 (0.49,1.98)	1.43 (0.87,2.35)	Ref	1.00 (0.65,1.54)
RR, ††Adj. Model 2	0.74 (0.21,2.66)	Ref	0.98 (0.49,1.98)	1.40 (0.85,2.3)	Ref	0.98 (0.64,1.50)

	hCG detected Loss			Clinical Loss		
	Low AMH <1.0 ng/ml	**Normal AMH 1.0-3.5 ng/ml**	**High AMH >3.5 ng/ml**	**Low AMH <1.0 ng/ml**	**Normal AMH 1.0-3.5 ng/ml**	**High AMH >3.5 ng/ml**
Last loss within prior one year (n=946), Experienced a loss - no. (%)	2 (13.3)	8 (7.4)	3 (4.0)	3 (20.0)	13 (12.0)	6 (7.9)
RR, Unadj.	0.79 (0.24,2.62)	Ref	1.02 (0.51,2.04)	1.33 (0.82,2.16)	Ref	1.15 (0.82,1.62)
RR, *Adj. Model 1	0.76 (0.28,2.03)	Ref	1.11 (0.64,1.91)	1.24 (0.77,2.01)	Ref	1.2 (0.85,1.68)
RR, ††Adj. Model 2	0.83 (0.30,2.27)	Ref	1.05 (0.61,1.83)	1.26 (0.78,2.03)	Ref	1.22 (0.87,1.71)
Last loss ≥ one year prior (n=237), Experienced a loss - no. (%)	3 (3.2)	18 (4.4)	20 (5.9)	3 (20.0)	13 (12.0)	6 (7.90)
RR, Unadj.	0.84 (0.30,2.31)	Ref	1.06 (0.61,1.84)	1.36 (0.63,2.93)	Ref	0.68 (0.30,1.55)
RR, *Adj. Model 1	1.42 (0.49,4.11)	Ref	0.63 (0.22,1.79)	0.92 (0.39,2.17)	Ref	0.78 (0.36,1.69)
RR, ††Adj. Model 2	0.79 (0.27,2.30)	Ref	0.82 (0.3,2.28)	0.8 (0.35,1.85)	Ref	0.88 (0.43,1.80)

Relative Risk (RR) presented as estimate (95% confidence interval).

***Adjusted for age**

†Adjusted for age, race, BMI, treatment, income, parity, number of previous losses, recency of loss

††Adjusted for age, race, BMI, treatment, income.

Table 3

AMH and aneuploidy of clinical loss

	Low AMH <1.0 ng/ml	Normal AMH 1.0-3.5 ng/ml	High AMH >3.5 ng/ml
Experienced a loss with aneuploidy - no. (%)	5 (45.5)	16(64.0)	8(42.1)
RR, Unadj.	1.03 (0.84,1.27)	Ref	0.67 (0.46,0.97)
RR, *Adj. Model 1	1.01 (0.80,1.29)	Ref	0.68 (0.47,0.98)
RR, †Adj. Model 2	1.02 (0.88,1.20)	Ref	0.84 (0.67,1.06)

Relative Risk (RR) presented as estimate (95% confidence interval).

***Adjusted for age**

†Adjusted for age, race, BMI, treatment, income, parity, number of previous losses, recency of loss;