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Published in:
Reproductive BioMedicine Online

DOI (link to publication from Publisher):
10.1016/j.rbmo.2023.01.023

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

RBMO

ARTICLE

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BIOGRAPHY

Sofie Bliddal is a medical doctor and earned her PhD studying thyroid function in pregnancy. She is currently working as a full-time researcher at the Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark. Her primary research interests are the interplay between hormonal aberrations, immune dysregulation and reproductive failure.

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KEY MESSAGE

In women with unexplained recurrent pregnancy loss (RPL), anti-Müllerian hormone (AMH) was not associated with the chance of live birth in the next pregnancy, achieved by either natural conception or assisted reproductive technology. Screening for AMH in women with RPL is not supported by current evidence.

ABSTRACT

Research question: Is anti-Müllerian hormone (AMH) associated with live birth rate (LBR) in women with unexplained recurrent pregnancy loss (RPL)?

Design: Cohort study of women with unexplained RPL attending the RPL Unit, Copenhagen University Hospital, Denmark, between 2015 and 2021. AMH concentration was assessed upon referral, and LBR in the next pregnancy. RPL was defined as three or more consecutive pregnancy losses. Regression analyses were adjusted for age, number of previous losses, body mass index, smoking, treatment with assisted reproductive technology (ART) and RPL treatments.

Results: A total of 629 women were included; 507 (80.6%) became pregnant after referral. Pregnancy rates were similar for women with low and high AMH compared to women with medium AMH (81.9, 80.3 and 79.7%, respectively) (low AMH: adjusted odds ratio [aOR] 1.44, 95% confidence interval [CI] 0.84–2.47, $P = 0.18$; high AMH: aOR 0.98, 95% CI 0.59–1.64, $P = 0.95$). AMH concentrations were not associated with live birth. LBR was 59.5% in women with low AMH, 66.1% with medium AMH and 65.1% with high AMH (low AMH: aOR 0.68, 95% CI 0.41–1.11, $P = 0.12$, high AMH: aOR 0.96, 95% CI 0.59–1.56, $P = 0.87$). Live birth was lower in ART pregnancies (aOR 0.57, 95% CI 0.33–0.97, $P = 0.04$) and with higher numbers of previous losses (aOR 0.81, 95% CI 0.68–0.95, $P = 0.01$).

Conclusion: In women with unexplained RPL, AMH was not associated with the chances of live birth in the next pregnancy. Screening for AMH in all women with RPL is not supported by current evidence. The chance of live birth among women with unexplained RPL achieving pregnancy by ART was low and needs to be confirmed and explored in future studies.

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KEYWORDS
AMH
Anti-Müllerian hormone
Assisted reproductive technology
Pregnancy
Recurrent miscarriage
Recurrent pregnancy loss

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Declaration: The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Anti-Müllerian hormone (AMH) is a homodimeric glycoprotein produced by the granulosa cells of preantral and antral follicles and is well established as a measure of the ovarian reserve (*Dewailly* et al., *2014*). Contrary to measures of FSH and oestradiol, AMH is mainly cycle independent (*Fanchin* et al., *2003*; *Hehenkamp* et al., *2006*; *La Marca* et al., *2007*; *van Disseldorp* et al., *2010*). As such, it is an appealing clinical biomarker to guide fertility treatment and optimize ovarian stimulation protocols (*Broer* et al., *2011*).

Abnormal concentrations of AMH are found in distinct populations of fertility patients (*Broekmans* et al., *2009*). In women with polycystic ovary syndrome (PCOS), AMH concentrations are usually high due to the excessive number of small antral follicles (*Abbara* et al., *2019*; *Teede* et al., *2019*). Low concentrations of AMH have been demonstrated in women with premature ovarian failure and in (previous) cancer patients with chemotherapy-induced damage to the ovaries (*Dewailly* et al., *2014*; *Knauff* et al., *2009*).

With increasing age, AMH concentrations decrease, as does the chance of conception per cycle, while pregnancy loss rates increase (*Kelsey* et al., *2011*). At 20–24 years of age, 8.9% of pregnancies were shown to result in a spontaneous pregnancy loss, while this prevalence rapidly increased after the age of 45 to approximately 74.7% (*Nybo Andersen* et al., *2000*). In patients undergoing IVF treatments, AMH concentrations have been debated as a prognostic factor for the chance of a live birth (*Alson* et al., *2018*; *Gat* et al., *2017*; *Iliodromiti* et al., *2014*; *Jiang* et al., *2018*; *Peuranpää* et al., *2020*; *Shim* et al., *2015*; *Tal* et al., *2015*). A recent meta-analysis demonstrated an association between low AMH and the risk of pregnancy loss in patients achieving pregnancy by treatment with assisted reproductive technology (ART) (*Busnelli* et al., *2021*). It is noteworthy that the only prospective study included in the meta-analysis failed to demonstrate such an association (*Busnelli* et al., *2021*). While prognostic outcomes have been thoroughly investigated in infertile women, data are lacking in women with recurrent pregnancy loss (RPL).

RPL affects approximately 2% of all women and in most of these women no explanation can be identified (*Ford and Schust, 2009*; *Jaslow* et al., *2010*; *Stephenson and Kutteh, 2007*). A systematic review demonstrated an increased risk of diminished ovarian reserve (including that of lower AMH concentrations) in 155 women with RPL compared to 158 women without RPL (*Bunnewell* et al., *2020*). In another recent study, the proportion of women with a low AMH increased with an increasing number of previous pregnancy losses, also when stratifying results according to the women's age (*Tan* et al., *2022*). However, while there may be an association between AMH concentrations and women diagnosed with RPL, the clinically most important issue is whether there is an association with the risk of yet another pregnancy loss. It is postulated that AMH concentration is associated with the chance of live birth in the next pregnancy achieved in women with unexplained RPL.

The objective of this study was to investigate the association of AMH with the chance of live birth in a large cohort of women with unexplained RPL.

MATERIALS AND METHODS

Participants

The present study is a cohort study of all women attending the Recurrent Pregnancy Loss Unit, a tertiary referral centre with patient uptake from all of Eastern Denmark, at the Copenhagen University Hospital (Rigshospitalet) between June 2015 and December 2021. Women could be referred to the unit if they had had three or more consecutive pregnancy losses or two consecutive late pregnancy losses or stillbirths. As previously described in a study on thyroid peroxidase antibodies (including some of the women included in the present study; *Bliddal* et al., *2019*), all women underwent extensive examinations upon referral to investigate potential explanations for RPL, including antiphospholipid syndrome, severe uterine abnormalities, chromosomal abnormalities, and thyroid autoimmunity or disease (*Bliddal* et al., *2019*). Antiphospholipid syndrome was defined as either positivity for lupus anticoagulant or anticardiolipin antibodies in two separate blood samples drawn at least 12 weeks apart. Thyroid autoimmunity was defined as positivity for thyroid peroxidase antibodies (cut-off 60 mIU/l, Kryptor immunofluorescence assay). Both the woman and her male partner were screened for clinically significant chromosomal abnormalities. In the case of women achieving pregnancy by sperm donation, paternal chromosomes were assumed to be normal as karyotype is performed in all sperm donors in Denmark.

Based on these examinations, women with any of the following were excluded: no RPL (fewer than three previous pregnancy losses); three or more previous live births; pregnancies achieved by egg donation; no available AMH measurement; or explained RPL (uterine malformation, clinically significant parental chromosomal abnormality, antiphospholipid syndrome, or thyroid disease including euthyroid women with positivity for thyroid peroxidase antibodies). Further, in the analyses of live birth, pregnancies complicated by risk factors unrelated to RPL were excluded (ectopic pregnancies, twin pregnancies, terminated pregnancies, molar pregnancies).

All women were offered monitoring of any achieved pregnancy by progesterone and sequential human chorionic gonadotrophin measurements every week, starting from a positive human chorionic gonadotrophin (HCG) urine test result, and ultrasound scans at gestational week 6 and every second week thereafter (Supplementary Figure 1). In case of a suspected pregnancy loss, the loss was confirmed by ultrasound scan(s) and measurements of HCG. In case of a viable pregnancy at gestational week 16, the women were referred for further obstetric follow-up at their local hospital for the remainder of the pregnancy. In terms of treatments offered to women with unexplained RPL, i.v. immunoglobulin (Privigen®, CSL Behring GmbH, Germany) was offered if the woman had a minimum of three consecutive unexplained pregnancy losses in pregnancies achieved by IVF or intracytoplasmic sperm injection, in cases of secondary RPL with five or more consecutive losses, or to women with a non-thyroidal autoimmune disease (rheumatoid arthritis, Crohn's disease, ulcerative colitis or myasthenia gravis) (*Christiansen* et al., *2015*, *2019*; *Egerup* et al., *2015*). In women achieving pregnancy by IVF or intracytoplasmic sperm injection,

prednisolone was given together with i.v. immunoglobulin. Hydroxychloroquine (Plaquenil®, Sanofi, Paris, France) was offered to women with a minimum of four consecutive losses (off-label before 2018 and from 2018 in an ongoing randomized controlled trial). In case of other treatments initiated at fertility clinics, such treatment was continued as prescribed by fertility doctors.

AMH analyses

AMH was measured at the Department of Clinical Biochemistry, Copenhagen University Hospital (Rigshospitalet and Hvidovre), by the Roche Elecsys assay on Cobas 8000 (Roche Diagnostics, Basel, Switzerland). The intermediary precision (coefficients of variation) was at 13 pmol/l, 7% and at 39 pmol/l, 7%. The analytical sensitivity was 0.07 pmol/l. Local validation established a functional assay sensitivity (corresponding to an intermediary precision of 25%) to 0.21 pmol/l. In categorical analyses, definitions of AMH were based on AMH measurements from women with regular menstrual cycles achieving pregnancy without ART (lower tertile: ≤10 pmol/l, medium tertile: ≥11 and <21.2 pmol/l, highest tertile: ≥21.2 pmol/l). Although most analyses in the present manuscript were categorical (see Statistics section), it was decided to include AMH values below 0.21 as absolute values of 0.20 pmol/l in continuous analyses, as it was believed the women with very low values represented important biological information.

Statistical analyses

The primary outcome of this study was live birth in the first pregnancy after referral, so each patient was only included once in analysis. Multiple logistic regression analyses were applied to further explore potential predictors of pregnancy and live birth. Besides AMH group (low, medium and high) as the main exposure, possible confounders were included: maternal age at referral (in years), previous number of losses, body mass index (BMI), smoking and paternal age for both outcomes. In the logistic regression model for chance of pregnancy after referral, irregular menstrual cycle (yes = 1, no = 0) was also included as covariate, and in the model for live birth, pregnancy by ART (IVF or intracytoplasmic sperm injection) (yes = 1, no = 0) and treatment with i.v. immunoglobulin (yes = 1, no = 0), prednisolone (yes = 1, no = 0) or hydroxychloroquine (yes = 1, no = 0) were included. Smoking was defined as ever having smoked (yes = 1, no = 0) in descriptive AMH analyses and as smoking during pregnancy (yes = 1, no = 0) in analyses of live birth in the first pregnancy after referral. An interaction term between ART and treatment with i.v. immunoglobulin (see treatment indication above, therefore substantial overlap with patients having i.v. immunoglobulin and undergoing ART) was explored and turned out to be significant, after which it was included in the final logistic regression model. Missing data were not replaced, but differences between subgroups with or without missing data were explored (Supplementary Tables 1–3). Last data extraction was on 6 December 2021, corresponding to a minimum follow-up time of 1 year after referral (median follow-up 47 months, range 12–107).

Bonferroni correction was applied to adjust for pairwise comparisons of the low/high AMH group to the medium AMH group in the primary analyses (i.e. a *P*-value of ≤0.025 was considered significant).

Sensitivity analyses were predefined and included other definitions of abnormal AMH; according to the manufacturer's documentation of age-dependent reference ranges, percentile-based cut-offs for 2.5–97.5 in women with regular menstrual cycles and no need for ART, and low AMH defined by 1 ng/ml, equivalent to 7.14 pmol/l as used in a few previous studies of AMH. Furthermore, the live birth analysis was repeated, splitting results in women achieving pregnancy by ART or naturally, respectively.

Statistical analyses were performed in SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). Figures were prepared in Microsoft Excel and SPSS Version 25.

Ethical approval

All data were collected and stored in a secure database with approval from the Danish Data Protection Agency (file number RH-2017-315 I suite 05939, 25 October 2017). Data were entered by the clinical staff and validated by research associates at the department and, for the purpose of this study, by SB and HSN with a focus on AMH and pregnancy outcome.

RESULTS

A total of 1035 women attended the unit, of which 699 (67.5%) were eligible for inclusion, and of these 629 (90.0%) had a measurement of AMH. FIGURE 1 is a flow chart of the inclusion process. There were no differences in characteristics between women with and without AMH measurement (Supplementary Table 1). Among the 629 women, 222 (35.3%) had previously had a live birth, the mean age was 33.5 years (SD 4.4), and the median number of previous losses was 3 (interquartile range [IQR] 3–4).

AMH concentrations and demographics

Characteristics of the included women according to AMH tertiles are presented in TABLE 1. The median AMH concentration was 16.0 pmol/l (lower tertile 12.0 pmol/l, upper tertile 22.0 pmol/l). All of the 82 women reporting an irregular menstrual cycle had oligomenorrhoea, of whom 58 (70.7%) had high AMH, and 18 (22.0%) had medium AMH. Of those reporting of an irregular cycle, six women (7.3%, two with medium AMH and four with high AMH) were taking hormonal contraceptives or metformin at the time of referral to control their menstrual cycle. PCOS had been previously diagnosed in 18 (2.9%) of the women, of whom 16 had high AMH concentrations.

Pregnancy after referral

In total, 507 (80.6%) women achieved a pregnancy after referral (56.1% within 3 months, 74% within 6 months, and all within 1 year). The proportions were similar between women with low AMH (81.9%), high AMH (80.3%) and medium AMH (79.7%). Women without a pregnancy after referral had a higher BMI ($P < 0.001$) and higher number of previous pregnancy losses ($P = 0.02$), but did not otherwise differ in characteristics including AMH concentrations (see Supplementary Table 2). Thus, the adjusted odds of achieving a pregnancy were also similar (low versus medium AMH adjusted odds ratio (aOR) 1.44, 95% CI 0.84–2.47, $P = 0.18$; high versus medium AMH: aOR 0.98, 95% CI 0.59–1.64, $P = 0.95$).

Of the 507 women with a pregnancy after referral, 479 women were eligible for outcome analyses (FIGURE 1). Among the 28 women excluded from the outcome analyses, fewer had regular menstrual cycles (71.4% versus 88.0%, $P = 0.02$), and more had high AMH (64.3% versus 34.7% in included women, $P = 0.01$), but excluded women did not otherwise differ in demographics (Supplementary Table 3). The excluded women with high AMH were mainly excluded due to ectopic

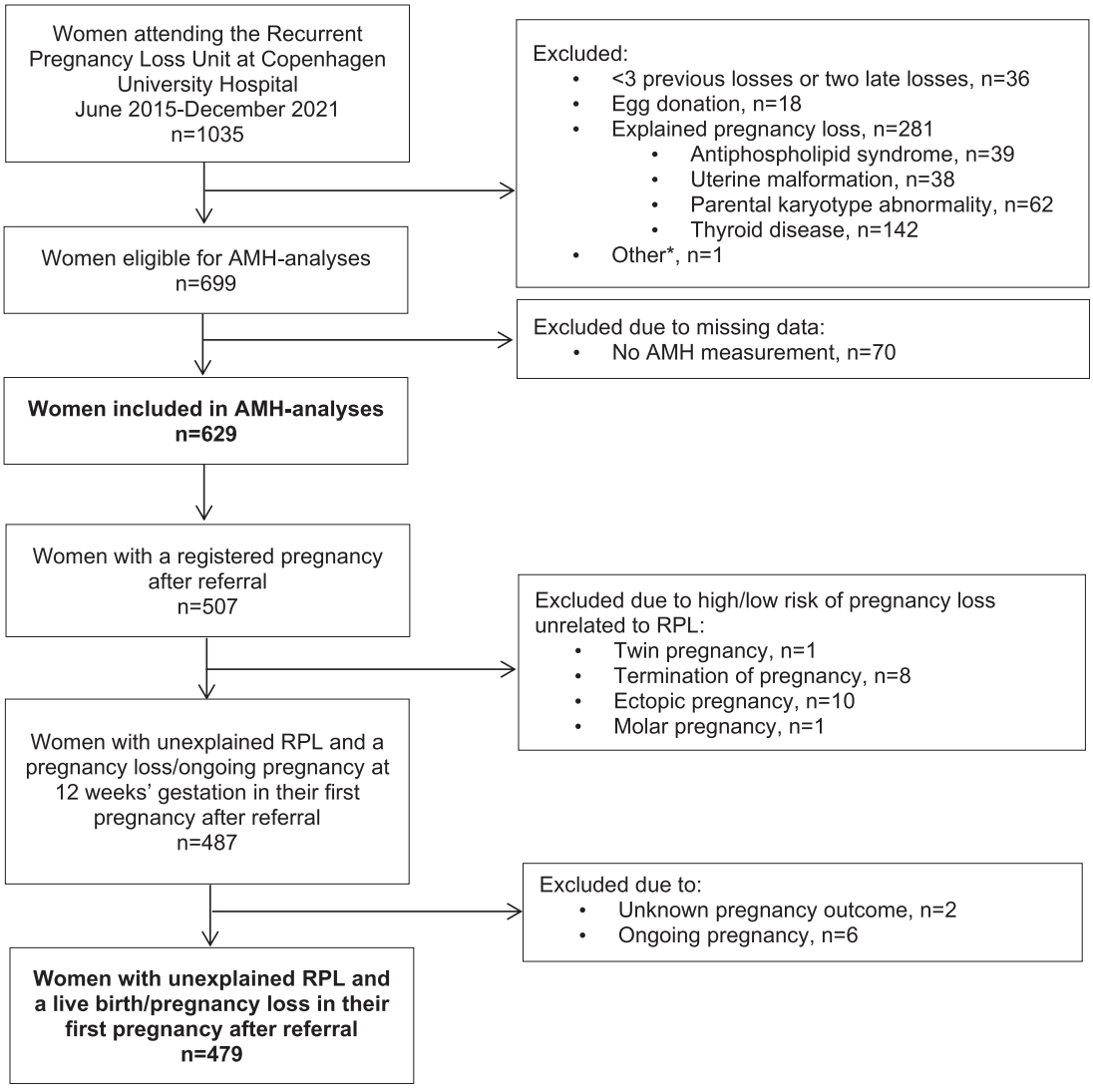

FIGURE 1 Flow chart of inclusion process. Inclusion process of women with unexplained RPL followed at the Recurrent Pregnancy Loss Unit between June 2015 and December 2021. AMH = anti-Müllerian hormone; RPL = recurrent pregnancy loss. *Excluded due to multiple severe maternal comorbidities.

TABLE 1 CHARACTERISTICS OF WOMEN WITH UNEXPLAINED RPL ACCORDING TO AMH CONCENTRATION AT REFERRAL

Characteristic	Low AMH *n* = 188 (29.9%)	Medium AMH *n* = 212 (33.7%)	High AMH *n* = 229 (36.4%)
Maternal age, years (mean, SD)	35.4 (4.2)	33.5 (4.2)	31.8 (4.2)[a]
Regular menstrual cycle	181 (96.8)	194 (91.5)	170 (74.6)[b]
BMI, kg/m^2 (median, IQR)	23 (21.0–26.3)	24 (21–26)	24 (22–28)[c]
Smoking (ever)	65 (34.8)	64 (30.2)	75 (32.8)
Number of previous losses (median, IQR)	3 (3–4)	3 (3–4)	3 (3–4)
Number of women with a previous live birth	73 (38.8)	79 (37.3)	70 (30.6)

Data are presented as *n* (%) unless otherwise stated.

AMH = anti-Müllerian hormone; BMI = body mass index; IQR = interquartile range; RPL = recurrent pregnancy loss.

[a] $P < 0.001$ by one-way analysis of variance across all three groups. Two women were missing information on cycle – one in low AMH group and one in high AMH group.

[b] $P < 0.001$ by chi-squared test across all three groups.

[c] With medium AMH as reference, high vs medium $P = 0.03$, low vs medium $P = 0.33$, by Mann–Whitney *U*-test.

pregnancies (8 ectopic pregnancies among the 18 excluded with high AMH [44.4%]), and thus 80% (8 out of 10) of all ectopic pregnancies were in women with high AMH.

Live birth according to AMH

The overall live birth rate (LBR) was 63.7%, and 73.8% of women achieved natural pregnancy. In the first pregnancy after referral, the median number of weeks of gestation in women who experienced pregnancy loss was 6.3 weeks (IQR 5.0–8.1 weeks) and in women with live births 39.6 weeks (IQR 38.4–40.6).

Of these women, in the 148 with a low AMH, LBR was 59.5% compared with 66.1% in the 165 women with a medium AMH (OR 0.75, 95% CI 0.48–1.19, $P = 0.23$, aOR with low AMH 0.68, 95% CI 0.41–1.11, $P = 0.12$) (TABLE 2). The women with low AMH were significantly older than those with medium AMH (mean [SD]: 35.0 [4.0] versus 33.2 [4.2] years, $P < 0.001$). Natural conception was achieved by 110 of the 146 (75.3%) women with low AMH (information on ART missing in two women). In the 166 women with a high AMH, LBR was 65.1% compared with 66.1% in women with a medium AMH (OR 0.96, 95% CI 0.61–1.51, $P = 0.85$, aOR 0.96, 95% CI 0.59–1.56, $P = 0.87$). Women with a high AMH were younger than women with a medium AMH (mean [SD]: 31.4 [4.1] versus 33.2 [4.2] years, $P < 0.001$). Natural conception was achieved by 119 of 164 (72.6%) women with high AMH (information on ART missing for two women).

Neither a low nor a high AMH were associated with live birth in the adjusted analyses (TABLE 2). The chance of live birth was significantly lower in women who had become pregnant by ART (OR 0.57, 95% CI 0.38–0.86, $P = 0.01$, aOR 0.57, 95% CI 0.33–0.97, $P = 0.04$), and women with a higher number of previous pregnancy losses (OR 0.87, 95% CI 0.76–1.00, $P = 0.05$, aOR 0.81, 95% CI 0.68–0.95, $P = 0.01$). Treatment with i.v. immunoglobulin was associated with a higher LBR in adjusted analyses (aOR 7.44, 95% CI 1.56–35.42, $P = 0.01$), with a significant interaction term with ART (aOR 0.08, 95% CI 0.01–0.60, $P = 0.01$).

The decline in AMH according to maternal age was similar in women who had a live birth and those who had another pregnancy loss, as illustrated in FIGURE 2A. The odds of live birth were not associated with AMH concentrations (log2 transformed AMH concentration: OR 1.09, 95% CI 0.94–1.27, $P = 0.25$, aOR 1.15, 95% CI 0.97–1.36, $P = 0.11$). Further, as illustrated by a receiver operating characteristic curve, AMH concentrations did not discriminate live birth well (FIGURE 2B).

Sensitivity analyses

Predefined sensitivity analyses were conducted. First, using the age-dependent reference ranges according to the manufacturer's documentation to define high or low AMH, there was no difference in the chance of live birth in the first pregnancy after referral (live birth with normal AMH [445 women] 63.8%, low AMH [17 women] 64.7% and high AMH [17 women] 58.8%, $P = 0.91$). Second, percentile-based cut-offs for the very lowest and highest AMH concentrations were applied. As illustrated in FIGURE 2A, even some women with the very lowest AMH concentrations did achieve a live birth. Of the 15 women with AMH concentrations below 1.9 pmol/l (corresponding to below the 2.5th percentile in women with regular cycle and no need for ART), 12 women (30–42 years of age) achieved a first pregnancy after referral (10 out of 12 naturally). Excluding one terminated pregnancy, five out of the remaining 11 pregnancies resulted in a live birth (45.5% compared with 64.0% of

TABLE 2 LIVE BIRTH IN THE FIRST PREGNANCY AFTER REFERRAL IN WOMEN WITH UNEXPLAINED RPL

Characteristic		Live birth *n* = 305 (63.7%)	Pregnancy loss *n* = 174 (36.3%)	OR (95% CI)	*P*-value	aOR (95% CI)[a]	*P*-value
Maternal age, years (mean, SD)		32.9 (4.3)	33.5 (4.6)	0.97 (0.93–1.01)	0.17	1.07 (0.73–1.56)	0.74
BMI (median, IQR)		23.0 (21.0–26.0)	24.0 (21.0–26.5)	0.98 (0.94–1.02)	0.34	0.99 (0.95–1.04)	0.79
Smoking during pregnancy		20 (6.6)	10 (5.7)	1.16 (0.53–2.54)	0.71	1.09 (0.46–2.58)	0.84
Number of previous losses (median, IQR)		3 (3–4)	3 (3–4)	0.87 (0.76–1.00)	0.05	0.81 (0.68–0.95)	0.01
ART treatment		66 (22.1)	57 (33.1)	0.57 (0.38–0.87)	0.01	0.57 (0.33–0.97)	0.04
AMH low[b]		88 (28.9)	60 (34.5)	0.75 (0.48–1.19)	0.23	0.68 (0.41–1.11)	0.12
AMH high[b]		108 (35.4)	58 (33.3)	0.96 (0.61–1.51)	0.85	0.96 (0.59–1.56)	0.87
Treatment during pregnancy	i.v. immunoglobulin	46 (15.1)	23 (13.2)	1.17 (0.68–2.00)	0.58	7.44 (1.56–35.42)	0.01
	Prednisolone	38 (12.5)	23 (13.2)	0.93 (0.54–1.63)	0.81	2.20 (0.72–6.70)	0.17
	Hydroxychloroquine	27 (8.9)	24 (13.8)	0.61 (0.34–1.09)	0.09	0.66 (0.36–1.24)	0.20
Paternal age, years (mean, SD)		33.5 (4.2)	34.1 (4.6)	0.97 (0.93–1.01)	0.16	0.93 (0.63–1.36)	0.70

Data are presented as *n* (%) unless otherwise stated.

P-values for the primary outcome of live birth according to AMH category were considered significant if $P \leq 0.025$ according to Bonferroni correction.

AMH = anti-Müllerian hormone; aOR = adjusted odds ratio; ART = assisted reproductive technology; BMI = body mass index; CI = confidence interval; IQR = interquartile range; OR = odds ratio.

[a] Odds ratio for live birth adjusted for covariates: AMH concentration (low vs medium vs high), age, previous losses, ART treatment, BMI, smoking during pregnancy, treatment with i.v. immunoglobulin, prednisolone, hydroxychloroquine and paternal age. Missing data from 17 women reduced the adjusted model by this number (by separated variables; BMI 7, smoking 2, ART 8). The model included an interaction term for ART and i.v. immunoglobulin with aOR 0.08, 95% CI 0.01–0.60, $P = 0.013$.

[b] Reference group 'AMH medium'.

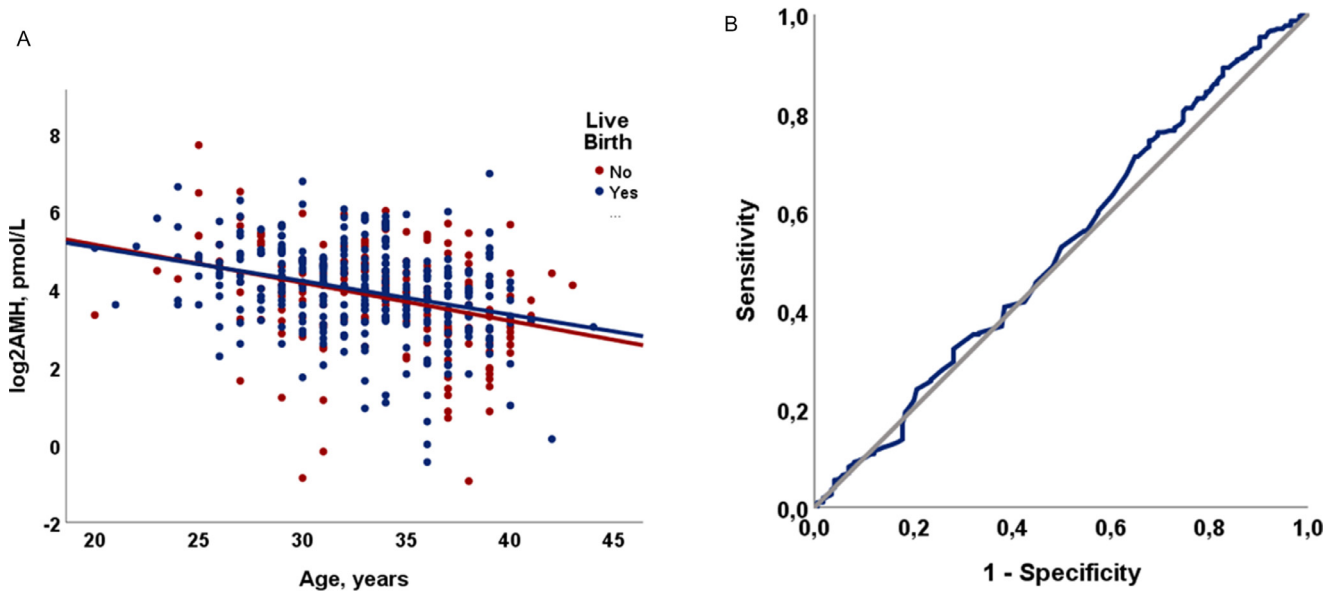

FIGURE 2 AMH concentrations and live birth. AMH concentration (log2 transformed) and chance of live birth in the first pregnancy achieved after referral in 479 women with unexplained RPL. (A) (log2 transformed) AMH concentration according to age at time of referral and outcome of the pregnancy. (B) Receiver operating characteristic curve illustrating the ability of (log2 transformed) AMH concentration to discriminate chance of live birth. AMH = anti-Müllerian hormone; RPL = recurrent pregnancy loss.

women with normal AMH, $P = 0.22$). Among the 29 women with AMH concentrations above 56 pmol/l (97.5th percentile in women with regular cycle and no need for ART), 23 achieved pregnancy (16 naturally) of whom two had extrauterine pregnancies and 14 out of the remaining 21 had live births (66.7% compared with 64.0% of women with normal AMH, $P = 0.80$).

Third, defining low AMH as below 1 ng/ml (equal to 7.14 pmol/l as used in a few previous studies) showed no difference in live birth either (56.6% of 76 women with low AMH compared to 65.0% in 403 women with AMH above 1 ng/ml, $P = 0.19$).

Given the finding of significantly lower LBR in women achieving pregnancy by ART, analyses were added to explore this. The gestational age at time of pregnancy loss did not differ between ART and non-ART pregnancies (median 6.0, IQR 4.9–7.9 versus median 6.6, IQR 5.0–8.6). As demonstrated in Supplementary Table 4, significantly fewer women achieving pregnancy by ART had given birth previously (primary RPL) ($P < 0.001$). However, dividing the adjusted analyses according to previous live birth or not, ART remained significantly associated with a low LBR in women without a previous live birth, but was not significant in women with a previous live birth (aOR 0.55, 95% CI 0.30–0.99, $P = 0.045$, and aOR 0.37, 95% CI 0.12–1.15, $P = 0.09$, respectively). Finally, when dividing analyses into women achieving pregnancy naturally or by ART, there were still no associations between live birth and low or high AMH in either subgroup (Supplementary Tables 5 and 6, respectively).

DISCUSSION

This large cohort study investigated characteristics of 629 women with unexplained RPL. No association was found between abnormal AMH concentrations and the odds of prospective live birth in the 479 women with a pregnancy after referral. However, women with a higher number of previous pregnancy losses and, especially, women achieving pregnancy by ART, had significantly lower LBR, which was somewhat ameliorated in those receiving i. v. immunoglobulin (interaction with ART being significant).

As AMH was postulated to be independently associated with live birth, age-adjusted AMH cut-offs were not used in the primary analyses. However, subgroups of women with RPL and premature ovarian insufficiency or PCOS could constitute different phenotypes with a different risk for pregnancy loss (*Mayrhofer* et al., *2020*; *Sjaarda* et al., *2018*). Interestingly, despite the exclusion of all women receiving egg donation, a low AMH concentration was not associated with a reduced chance of achieving pregnancy. In a study of healthy women, *Hagen* et al. *(2012)* found no reduction in pregnancy rate among women with low AMH concentrations. Thus, a low AMH outside of an ART setting does not seem to be strongly associated with either the chance of achieving pregnancy or of live birth.

A few other studies have investigated the association between AMH measurements and subsequent live birth in women with RPL. In accordance with the current findings, *Pils* et al. *(2019)* did not find a lower LBR according to AMH concentration in 94 women with unexplained RPL. The same conclusion was reached by *Leclercq* et al. *(2019)* in a case–control study comparing 188 unselected women with RPL to 376 age-matched parous women without pregnancy loss. Finally, two smaller studies also found comparable pregnancy loss rates between women with low and normal AMH (*McCormack* et al., *2019*; *Xiao* et al., *2016*). Contrary to the current findings, *Murugappan* et al. *(2019)* did find an association between AMH concentrations and reduced LBR in 155 women with RPL. This could be explained by differences in study design, such as inclusion of women with uterine factors or antiphospholipid syndrome, multiple pregnancies allowed per woman, and a follow-up period of only

12 months. Notably, low analytical accuracy and precision have challenged comparisons of studies involving AMH assays (*Victoria* et al., *2019*). New automated immunoassays have improved the analytical shortcomings, but the assay used must still be considered a limiting factor in comparing study results (*Nelson* et al., *2015*; *van Helden and Weiskirchen, 2015*; *Victoria* et al., *2019*).

Women with unexplained RPL constitute a small proportion of women of reproductive age. Phenotypical variation and differing study designs may explain the conflicting results on the association between AMH concentrations and prospective live birth in women with a healthy reproductive history, with only one or two previous pregnancy losses, or women undergoing ART treatment (*Hong* et al., *2020*; *Lyttle Schumacher* et al., *2018*; *Peuranpää* et al., *2020*; *Tarasconi* et al., *2017*; *Zarek* et al., *2016*). This study did not find an association with AMH and live birth, nor when dividing results in women with RPL achieving pregnancy naturally or by ART. Based on these findings, and in accordance with guidelines from the European Society for Human Reproduction and Embryology (*ESHRE Guideline Group on RPL* et al., *2018*), it is not thought that AMH should be measured in all women with RPL.

Notably, women achieving pregnancy by ART had odds ratios for live birth of 0.56 compared to those with natural pregnancies. Traditionally, ART has not been considered an independent risk factor in either women with RPL (*ESHRE Guideline Group on RPL* et al., *2018*) or in women undergoing ART compared with those achieving natural pregnancy (*Schieve* et al., *2003*; *Shevell* et al., *2005*). The women achieving pregnancy by ART were older, which could explain some of the increased risk of pregnancy loss. However, the association remained significant also when adjusting for maternal age in the regression model. The current study did find an increased chance of live birth after treatment with i.v. immunoglobulin (including a significant interaction term between ART and i.v. immunoglobulin). However, confidence intervals were wide, and subgroups were based on a low number of women. Previous studies of i.v. immunoglobulin in the setting of RPL have shown conflicting results (*Achilli* et al., *2018*; *Christiansen* et al., *2002*; *Egerup* et al., *2015*, *2022*; *Nyborg* et al., *2014*; *Wang* et al., *2016*; *Yamada* et al., *2022*). Although the association between ART and low LBR in the present study was robust in various sensitivity and subgroup analyses, this finding calls for confirmation in future studies, including exploration of specific RPL phenotypes and interventions that could improve prognosis. An ongoing randomized controlled trial is investigating the effect of i.v. immunoglobulin administration in women with RPL after ART (https://clinicaltrials.gov/ct2/show/NCT04701034).

There are strengths and limitations to this study. In particular, the large number of included women with unexplained RPL from a large tertiary setting with close follow-up provides important information on prospective live birth after referral. Although there were no differences in characteristics between the women with and without a registered first pregnancy after referral (Supplementary Table 2), some women may have failed to report a pregnancy to the clinic, thus inflicting bias. Further, whereas there were no trends towards lower birth rates among those with either low or high AMH concentrations, only five out of ten women with very low AMH concentrations achieved a live birth. Thus, power to detect significant differences in such small subgroups would require very large cohorts or meta-analyses, especially because women with low AMH concentrations were significantly older. Therefore, analyses would need adjustment for maternal age because the lower LBR is likely to reflect a negative impact of biological ageing (*Nelson* et al., *2013*).

In conclusion, this cohort study of a large number of women with unexplained RPL did not find an association with AMH concentrations and subsequent live birth. AMH should therefore not be included in routine screening of women with RPL. A remarkably lower LBR among women with unexplained RPL achieving pregnancy by ART needs to be confirmed and further explored in future studies.

DATA AVAILABILITY

Data can be made available upon reasonable request and legal permissions obtained

ACKNOWLEDGEMENTS

We owe great thanks to nurses Karen Kirchheiner Jensen, Marie Chonovitsch and Anne-Louise Lunøe for their endless efforts in taking care of the many women with RPL followed in the study unit. Ulla Feldt-Rasmussen's research salary is supported by a grant from Kirsten and Freddy Johansen's Foundation.

AUTHOR ROLES

SB and HSN planned the study and drafted the first version of the manuscript. UFR and LMH provided expertise on the bioanalytical methodology. JLF supervised the statistical analysis plan. All authors made substantial contributions to the analysis or interpretation of data and the critical revision of the manuscript for important intellectual content. All authors approved the final submitted version.

FUNDING

The research and work related to the preparation of this manuscript has been kindly supported by the Copenhagen University Hospital Rigshospitalet, Musikforlæggerne Agnes and Knut Mørk's Foundation, Desiree and Niels Yde's Foundation, the Danish Medical Association's Research Foundation, the A. P. Møller Foundation for the Advancement of Medical Science, the Lundbeck Foundation, the Danish Thyroid Patient Association and the Novo Nordisk Foundation. None of the funding sources had any influence on the design and conduct of this study, on the analysis and interpretation of results or on the decision to publish this manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2023.01.023.

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Received 17 October 2022; received in revised form 16 December 2022; accepted 25 January 2023.