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REVIEW ARTICLE

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The relationship between anti-Müllerian hormone, body mass index and weight loss: A review of the literature

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Summary

Anti-Müllerian hormone (AMH) is commonly used as a proxy for ovarian reserve due to its secretion by antral follicles. It is considered a metric for prediction of ovarian response to certain assisted reproduction therapies. As obesity has a negative impact on fertility, it is important to establish whether obesity-induced hormonal changes influence AMH levels, if and how weight loss affects AMH, and if that influence represents altered reproductive function. The aim of this study was to review the existing literature on the effects of body mass index and weight loss on AMH levels. A PubMed literature keyword search with relevant terms was performed to identify studies that have reported on the AMH/BMI relationship in cohorts with or without polycystic ovarian syndrome (PCOS). A second search was performed to gather publications on weight loss and AMH. Both searches were filtered for all full-text, English-language, adult-female and human-only literature through 1 January 2022. The relationship between AMH and body mass index (BMI) in reproductive-aged women remains inconclusive, with studies in women with and without PCOS producing mixed results. Research in this area is currently limited by failure to analyse the full spectrum of obesity, hindering generalization to a global population increasingly affected by the condition. Some authors pointed to evidence of race/ethnicity as a confounding factor of the relationship, but results between studies are contradictory. Limited evidence on weight loss suggests it may decrease AMH levels despite improving fertility outcomes, particularly after bariatric surgery. The impact of BMI and weight loss on AMH levels has not been conclusively established. Future studies will require appropriate design and sample size calculations, consideration for additional potential confounding factors and inclusion of higher BMIs and a thorough analysis of the full range of obesity.

KEYWORDS

anti-Müllerian hormone, body mass index, fertility, obesity, PCOS

What is already known about this subject?

- Obesity has a detrimental effect on fertility.
- AMH is produced by preantral and small antral follicles and is used as a marker for ovarian reserve as well as to predict success of IVF.

What this study adds?

- A summary and analysis of the research on the impact of body mass on AMH, in both women with and without PCOS.
- A summary and analysis of the research on the impact of weight loss on AMH.
- Proposed mechanisms for potential associations and suggestions for future research.

1 | INTRODUCTION

The relationship between anti-Müllerian hormone (AMH) and body mass index (BMI) in reproductive-aged women is uncertain. Due to the known correlation of AMH with ovarian response, uncovering a link between the two would mark an important step toward understanding the connection between body mass and ovarian function.

In 2015, the Global Burden of Disease study found that obesity affected 603.7 million adults, with prevalence increasing worldwide, and a higher prevalence among women than men.[1] Elevated BMI is a risk factor for cardiovascular disease, diabetes, kidney disease and some cancers, as well as infertility. Its negative effects on reproductive function are thought to be primarily via endocrine mechanisms.[2]

AMH is a glycoprotein of the TGF-β family discovered in 1947 for its role in the regression of Müllerian ducts. The hormone was first detected in follicular fluid in the mid-1990s and was later demonstrated to be involved in folliculogenesis.[3] It is secreted principally by primary, preantral and early antral follicles, preventing excess follicular recruitment in a paracrine fashion. Because of its role in the pre-antral and antral stage follicle, it may serve as a surrogate marker of the follicular pool and is used as a metric for ovarian reserve and to predict response to in vitro fertilization (IVF). Serum concentrations of AMH are gonadotropin independent and remain relatively constant within and between menstrual cycles, making it a convenient and useful marker that typically decreases with age.[4] Ovarian reserve correlates inversely with age, but there is considerable variation in ovarian reserve among women of the same chronologic age. It is important to note that ovarian reserve refers to the number of oocytes remaining in the ovary, and that oocyte quantity differs from oocyte quality, which is the potential of a fertilized oocyte to result in a live-born infant, and the only current marker for quality is age.

Another common marker of ovarian reserve is antral follicle count (AFC), which is the sum of the number of antral follicles in both ovaries as observed with transvaginal ultrasonography during the early-follicular phase.[5] Although there is generally a positive correlation between AMH and AFC, at times they may conflict and these discordant results may complicate management.[6] As a result, AMH is a useful but imperfect proxy for ovarian reserve. For this reason, it is essential to establish how BMI might affect AMH and if that effect represents altered reproductive function, or whether AMH is simply not a useful marker in women with obesity.

Many existing studies exploring the relationship between serum AMH concentration and BMI involve patient populations with polycystic ovarian syndrome (PCOS). PCOS is an endocrine disorder defined by the presence of two of three Rotterdam criteria: ovulatory dysfunction, hyperandrogenism and polycystic ovaries on ultrasound, determined by the existence of at least 12 follicles in each ovary between 2 and 9 mm in diameter, or ovarian volume > 10 ml.[7] As antral follicles produce AMH, high hormone levels correlate with increased antral follicle count.[8] This results in characteristically elevated AMH levels in patients with PCOS.[9] The aim of this article is to report on the current literature, differentiating between research with PCOS and non-PCOS populations, and to summarize the data on the effect of weight loss on AMH levels.

2 | METHODS

A PubMed search was done with the search terms "((anti-mullerian hormone) OR (AMH)) AND (BMI) AND ((obesity) OR (obese) OR (overweight))" to find relevant literature published prior to 1 January 2022. In the search, non-English and non-human studies were excluded, while only full-text studies of adult women were included. This filtered search yielded 63 results which underwent title and abstract screening. Editorials, commentaries, letters, book chapters and other literature reviews were excluded. Peer-reviewed literature, original research reports, cohort studies and cross-sectional studies were included. Cohorts non-representative of the general population intended for this investigation were excluded, such as those with potentially biasing comorbidities, including those undergoing IVF treatments with ovarian stimulation. Studies of postmenopausal and recently pregnant (<3 months) women were excluded. Only studies using the World Health Organization definition of overweight as a BMI of 25–30 kg/m^2 and obesity as a BMI of 30 kg/m^2 and above were included. Studies that analysed the BMI and AMH relationship in cohorts of unknown PCOS status were excluded. We defined a non-PCOS cohort as excluding or controlling for PCOS patients. Where patients with PCOS are included but controlled for, this information is reported in Table 1. Using these criteria, 16 studies

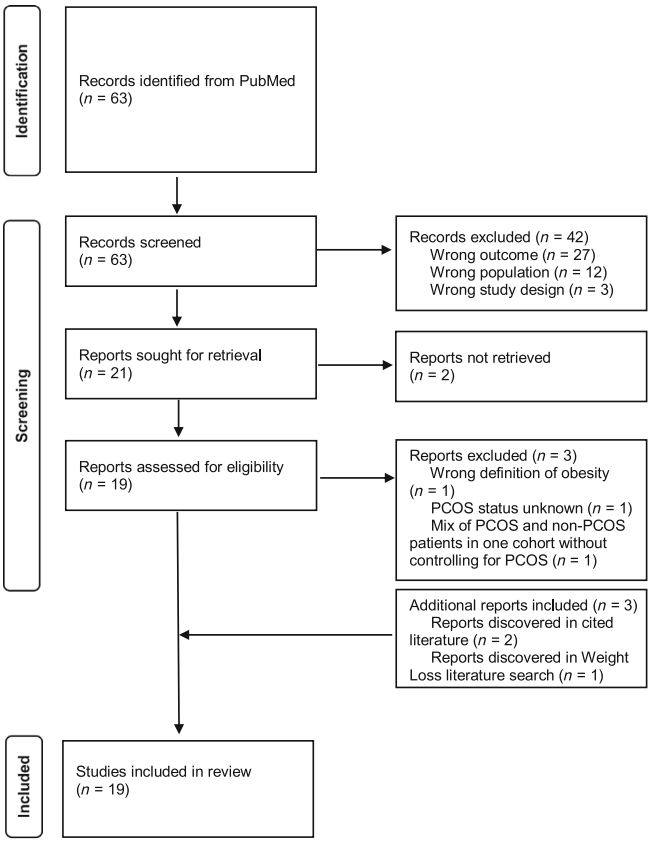

FIGURE 1 PRISMA flow diagram for the literature search for an association between AMH and BMI.

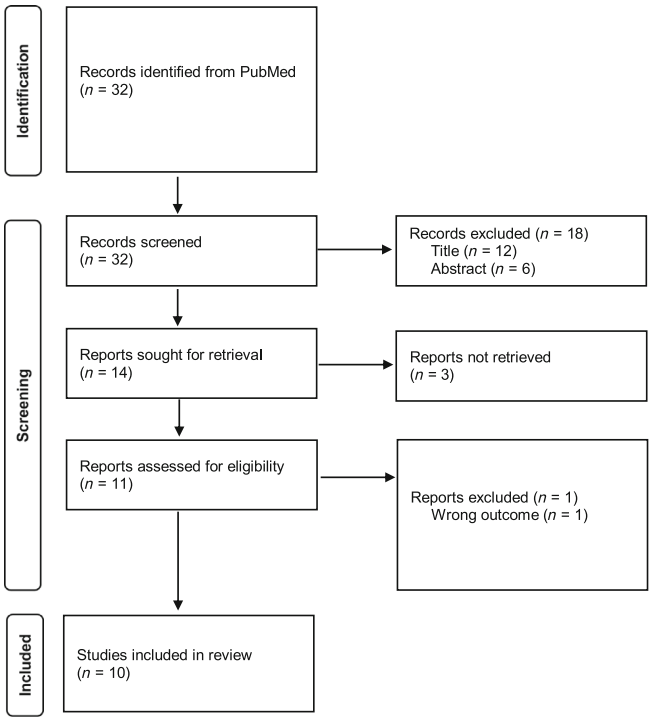

FIGURE 2 PRISMA flow diagram for the literature search for an association between weight loss and change in AMH.

assessing the relationship between AMH and BMI were selected for inclusion. Two additional relevant publications referenced within search-identified literature were also included for completeness, as well as one found via our search for weight loss data, described below. Figure 1 illustrates the review process for these studies.

A PubMed literature search was performed to find full-text, English-language studies of AMH levels after weight loss in adult female patients with the human-only search terms "(((weight loss) OR (weight-loss) OR (bariatric)) AND ((AMH) OR (antimullerian hormone))" which produced 32 results through 1 January 2022. Studies investigating weight loss drugs were excluded for consistency, while studies on bariatric weight loss surgery, caloric restriction or diet and exercise were included. Ten studies were selected for inclusion. One of these was found to present data on the association of BMI and AMH prior to weight loss and was included in that analysis (Figure 1). Figure 2 illustrates the review process for these studies.

3 | RESULTS

3.1 | Studies of AMH in women without PCOS

The current evidence on the association between BMI and serum AMH levels in women without PCOS is inconclusive but trending toward no relationship. Table 1 summarizes this evidence: 8 studies indicate no association,[10–17] while 2 found a positive association within at least one cohort[18,19] and 4 determined an negative relationship within at least one cohort.[20–23] A 2020 study by Jaswa et al. found that AMH serum levels declined significantly with increasing BMI in the population without obesity (BMI <30 kg/m^2).[21] Jaswa et al. also took plasma volume into consideration and found that no dilutional effects contributed to the significant negative relationship. Jaswa et al. did not find a relationship between BMI and AMH in its cohort with obesity, which had a mean BMI of 36.94 kg/m^2. In contrast to the significant correlation denoted above, other studies' explorations have returned no association. Hardy et al. was one of such studies that determined no correlation.[11] However, as obesity has a documented negative impact on fertility, the postpartum status of all patients in Hardy et al. is to be noted when considering the generalizability of the cohort's reproductive markers.[2] The study compared AMH levels between normal-weight groups and groups with a BMI of at least 40 kg/m^2; thus, these results agree with Jaswa et al.'s findings that a relationship between AMH and BMI does not exist at obese BMIs.[21] Although working with a smaller sample size of 26 patients, Chiofalo et al.[16] also found no correlation in this group with a mean BMI of 46 kg/m^2, as did Bhandari et al. with a non-PCOS sample of 32 patients with mean BMI 45.03 kg/m^2. Although their PCOS cohort as a whole also revealed no association, Bhandari et al.'s results are complicated by their finding that at BMIs above 51 kg/m^2, in a mixed cohort of patients with and without PCOS, AMH levels fell significantly.[17]

TABLE 1 Summarized relationships between BMI and AMH in non-PCOS populations

Publication	Cohort(s)	BMI range (BMI mean) (kg/m^2)	# Patients	Age range (mean age) (years)	Findings
Albu et al.[19]	All, with underweight, normal weight, with overweight	With Underweight: <18.5 (17.7) Normal weight: ≥18.5 and <25 (21.3) With Overweight: ≥25 (28.3)	All: 2204 With Underweight: 227 Normal weight: 1543 With Overweight: 434	Not reported (34.58)	A significant positive relationship between BMI and AMH was found overall ($\beta = 0.059$; $p < .005$) and within the normal-weight cohort when adjusted for age ($\beta = 0.056$; $p < .05$), but not within the underweight and overweight cohorts.
Skałba et al.[18]	All, without overweight, with overweight	All: (25.8) Without overweight: ≥18.5 and <25 (20.6) With overweight: ≥ 25 (28.5)	All: 50 Without overweight: 28 With overweight: 22	Not reported (25.8)	No significant relationship was found overall or within the cohort with overweight. A significant positive relationship between BMI and AMH was found within the cohort without overweight ($r = .37$; $p < .05$).
Bernardi et al.[20]	All, BMI ≥25 and <40, BMI 40+ (All patients African American)	All: 15.9–79.4 (Not reported; median = 32.4)	All: 1654 BMI ≥25 and <40: 932 BMI 40 to <45: 201 BMI 45+: 186	23–25 (28.7)	A significant negative relationship between BMI and AMH was found overall ($\beta = -0.015$; $p < .0001$) and within the BMI 40 to <45 cohort ($\beta = -0.265$; $p = .0091$) and BMI 45+ cohort ($\beta = -0.372$; $p = .0005$), but not within the BMI ≥25 and <40 cohort when controlled for age, oral contraceptive use and abnormal menstrual bleeding. These findings persisted with exclusion of the 3.2% of participants with PCOS.
Jaswa et al.[21]	All, without obesity, with obesity	All: 15.8–53.9 (26.7) Without obesity: <30 (Not reported) With obesity: 30.0–53.4 (36.9)[a]	All: 870 Without obesity: 664 With obesity: 206	25–40 (33.0)	A significant negative relationship between BMI and AMH was found overall when controlled for age, race, smoking and study centre ($\beta = -0.019$; $p < .001$), and when not ($r = -.08$; $p < .001$). A significant negative relationship was found in the group without obesity ($r = -.11$; $p = .01$) but not in the group with obesity.
Moy et al.[22]	Caucasian (C), African American (AA), Asian American (A), Hispanic (H)	C: (25.9) AA: (30.7) A: (22.9) H: (28.1)	C: 142 AA: 93 A: 34 H: 53	16–46 C: (36.3) AA: (37.6) A: (35.8) H: (38.1)	A significant negative relationship between BMI and AMH was found among Caucasian women ($\beta = -0.17$, $p = .01$) when controlled for age, smoking and presence or absence of PCOS. When women with PCOS were excluded, the results were the same ($\beta = -0.16$, $p = .037$). No significant relationship was found within African American, Asian American or Hispanic cohorts.

TABLE 1 (Continued)

Publication	Cohort(s)	BMI range (BMI mean) (kg/m^2)	# Patients	Age range (mean age) (years)	Findings
Olszanecka-Glinianowicz et al.[23]	Without obesity, with obesity	With obesity: Not reported (33.4) Without obesity: Not reported (22.2)	With obesity: 36 Without obesity: 31	Not reported (25.7)	Significantly lower AMH levels found in the cohort with obesity compared with the cohort without obesity ($p < 0.05$).
Bhandari et al.[17]		Not reported (45.03)	32	20–35 (Not reported)	No significant relationship found.
Chiofalo et al.[16]		Not reported (46)	26	18–39 (33)	No significant relationship found.
Halawaty et al.[10]	Without obesity, with obesity	Without obesity: <30 (25.6) With obesity: 30–35 (32.9)	Without obesity: 50 With obesity: 50	38–48 (46.1)	No significant relationship found between the cohorts with and without obesity.
Hardy et al.[11]	Without overweight, with obesity (All patients 3 months postpartum)	Without overweight: ≤25 With obesity: ≥40	Without overweight: 38 With obesity: 31	Not reported (33.97)	No significant relationship found between the non-overweight cohort and cohort with obesity.
Lefebvre et al.[12]		17.9–37.0 (23.0)	137	22–35 (29.0)	No significant relationship found.
Sahmay et al. (2012)[13]	Without obesity, with obesity	Without obesity: <30 (24.2) With obesity: ≥ 30 (33.6)	Without obesity: 222 With obesity: 37	Not reported (32.17)	No significant relationship found between the cohorts with and without obesity.
Shaw et al.[14]	All Caucasian	Not reported (25)	135	Not reported (41)	No significant relationship found.
Simões-Pereira et al.[15]		<40 (Not reported; median = 23)	951	Not reported (35)	No significant relationship found.

[a]Values obtained via correspondence with the author.

Rather than looking for a correlation, some studies compared average AMH levels between cohorts of different BMIs. Sahmay et al. compared AMH levels between groups with and without obesity and found no difference.[13] Conversely, Olszanecka-Glinianowicz et al. found a significant difference, with lower AMH levels in the group with obesity.[23] Despite different conclusions, the cohorts were similar between the studies: the two cohorts with obesity had a nearly identical mean BMIs, while the two cohorts without obesity had mean BMIs within 2 kg/m^2 (Table 1).

Differences in baseline AMH levels between races/ethnicities have been proposed. A 2015 study by Moy et al. found that among women without PCOS, BMI and AMH were negatively correlated among Caucasian women, but this relationship was not sustained among African American, Asian American and Hispanic women. Of note, the Asian American cohort had over four times fewer patients than the Caucasian group, and the mean BMI for Caucasian women in this study was 25.9 kg/m^2, while for African American and Hispanic women it was considerably higher: 30.7 and 28.1 kg/m^2, respectively.[22] In contrast, Shaw et al. conducted a 2011 study of 135 Caucasian, premenopausal women with an average BMI of 25 kg/m^2.[14] Findings demonstrated no correlation between AMH and BMI.

Bernardi et al. published contradictory results to Moy et al. in a 2017 study focused solely on African American women.[20] The researchers found that AMH and BMI were significantly negatively correlated. The researchers also stratified the 1654 participants by BMI from 25 to ≥45, with each stratum including a range of 5 kg/m^2. Their analysis returned a significant negative relationship only with BMIs of 40+, potentially contradicting aforementioned studies that found a relationship only among participants without obesity.

Interestingly, participants in Bernardi et al. were between ages 23 and 25 years old and self-reported their weights at age 18. Those who had obesity both at age 18 and at the time of the study had substantially lower AMH concentrations than those who reported normal weight at age 18, implying that duration of obesity may impact its effects.

3.2 | Studies of AMH in women with PCOS

Although AMH is characteristically increased in patients with PCOS, studies may point to the existence of a negative relationship. Table 2 summarizes the relevant studies, with 3 finding no association,[16,17,24] 1 finding a positive association within at least one cohort[18] and 7 reporting a significant negative relationship within at least one cohort.[12,21,23,25–28]

Jaswa et al. found a significant negative relationship overall in the population without obesity between BMI and AMH among women with PCOS.[21] However, unlike their non-PCOS group, this

TABLE 2 Summarized relationships between BMI and AMH in PCOS populations

Publication	Cohort(s)	BMI range (BMI mean) (kg/m^2)	# Patients	Age range (Mean age)	Findings
Skałba et al.[18]	All, without overweight with overweight	All: (24.1) Without overweight: ≥ 18.5 and <25 (21.1) With overweight: ≥ 25 (29.0)	All: 87 Without overweight: 54 With overweight: 33	Not reported (24.8)	A significant positive relationship between BMI and AMH was found in the cohort without overweight ($r = .37$; $p < .05$) but no significant relationship was found overall or within the cohort with overweight.
Chen et al.[25]		17.61–37.11 (Not reported; median = 23.05)	All: 99	21–35 (Not reported; median = 26)	Significant negative relationship between BMI and AMH ($r = -.213$; $p = .035$).
Feldman et al.[26]		Not reported (33)	252	Not reported (28.4)	Significant negative relationship between BMI and AMH ($r = -0.33$; $p < .0001$).
Freeman et al.[27]	All, with obesity, without obesity	Not reported (29.9)	All: 122	35–47 (Not reported)	Significantly lower AMH levels found in the cohort with obesity compared with the cohort without obesity ($p = .034$).
Jaswa et al.[21]	All, without obesity, with obesity	All: (35.1) Without obesity <30 (Not reported) With obesity: >30 (Not reported)	All: 640 Without obesity: 210 With obesity: 430	25–40 (30.0)	A significant negative relationship between BMI and AMH was found both when controlled for age, race, smoking and study centre ($\beta = -0.023$; $p < .001$), and when not ($r = -.19$; $p < .001$). A significant negative relationship was also found within the cohorts without ($r = -.38$; $p < .002$) and with ($r = -.1$; $p < .001$) obesity.
Kriseman et al.[28]		Not reported (29.9)	104	Not reported (31.0)	Significant negative relationship between BMI and AMH ($p = .002$) both when ($r = -.31$) and when not ($r = -.29$) controlled for age.
Lefebvre et al.[12]		18.5–41.0 (27.0)	554	20–33 (27.0)	Significant negative relationship between BMI and AMH ($r = -.177$; $p = .0001$).
Olszanecka-Glinianowicz et al.[23]		With obesity: Not reported (36.1) Without obesity: Not reported (21.3)	With obesity: 48 Without obesity: 39	Not reported (25.4)	Significantly lower AMH levels found in the cohort with obesity compared with the cohort without obesity ($p < .001$).
Bhandari et al.[17]		Not reported (42.52)	43	20–35 (Not reported)	No significant relationship found.
Chiofalo et al.[16]		Not reported (44)	29	18–39 (30)	No significant relationship found.
Sahmay et al. (2018)[24]		21–32 (26.3)	293	19–26 (22)	No significant relationship found.

relationship was maintained in the PCOS cohort with obesity. Lefebvre et al. and Kriseman et al. also found significant negative relationships, both with average study BMIs of <30 kg/m^2.[12,28] Skałba et al. demonstrated significance only in the normal-weight cohort and, like its non-PCOS cohort, this relationship was positive.[18]

In contrast to these studies with negative or positive AMH and MBI relationships is the 2017 study by Sahmay et al.[24] that investigated the relationship between serum AMH levels and insulin resistance in a group of 293 women with PCOS. The researchers did not find a relationship between serum AMH and BMI, although insulin resistance was more prevalent in women with BMI ≥ 25 kg/m^2 and AMH levels did increase in women with greater number of symptoms associated with PCOS. Although a large sample size was used, the maximum patient BMI was 32 kg/m^2.

3.3 | Effect of weight loss on AMH

The impact of weight loss, via surgical means or lifestyle modification, has also been studied as it pertains to AMH levels. Table 3 summarizes

TABLE 3 Effects of weight loss on AMH levels

Publication	Cohort and methods	Results
Al-Eisa et al.[42]	90 women underwent a 12-week exercise intervention; 30 of these were non-obese and without PCOS, 30 were obese with PCOS and 30 were obese without PCOS	After 12 weeks, all cohorts had a decrease in BMI ($p < .05$). The cohort without obesity or PCOS saw a significant rise in AMH while the cohorts with obesity with and without PCOS both saw a significant decrease in AMH levels ($p < .05$).
Bhandari et al.[17]	43 women with PCOS and 32 without underwent sleeve gastrectomy	BMI and AMH levels were significantly decreased in both groups of patients at 6 months post-operatively ($p < .001$).
Chiofalo et al.[16]	14 women with PCOS and 18 women without PCOS underwent either Roux-en-Y gastric bypass or sleeve gastrectomy	AMH levels were significantly decreased in patients with PCOS ($p = .02$) and without PCOS ($n = 0.04$) 12 months after bariatric surgery, with mean excess weight loss 65% ± 19%.
Foroozanfard et al.[34]	60 women with PCOS and overweight or obesity received one of two equicaloric diets, one of which was rich in fruits, vegetables, whole grains and low in fats and cholesterol (DASH diet)	Adherence to the DASH diet compared with the control resulted in a significant decrease in BMI ($p = .02$) and AMH ($p = .01$).
Milone et al.[31]	40 women with a history of assisted reproductive technology failure and idiopathic infertility underwent bariatric surgery	No significant change in AMH levels before and after surgery despite significant decrease in BMI ($p < .001$).
Merhi et al.[30]	7 women younger than 35 (PCOS = 1), 4 women older than 35 but premenopausal (PCOS = 1) and 5 postmenopausal women (PCOS = 0) underwent bariatric surgery	Only the group <35 years showed a significant change in AMH levels at an average of 87 days postoperatively. This change was negative ($p = .34$).
Moran et al.[35]	Women with overweight or obesity with ($n = 7$) and without ($n = 8$) PCOS participated in a 12-week intense exercise intervention	Women without PCOS had no change in AMH levels after the intervention ($p = .48$) while women with PCOS had a decrease in AMH ($p = .025$).
Nilsson-Condori et al.[32]	48 women (PCOS = 10) underwent very low-calorie diets prior to Roux-en-Y gastric bypass surgery	Median AMH levels rose significantly after very low-calorie diets ($p = .014$) but fell at 6 and 12 months postoperatively ($p = .001$) with mean excess weight loss 92.5% ± 20.1%.
Nybacka et al.[33]	57 women with overweight or obesity and PCOS were divided into intervention of diet, physical exercise or both for 4 months	Mean BMI decreased significantly in all 3 intervention groups. In the diet group, AMH decreased ($p < .01$) but not in the exercise or combined groups ($p = .53$ and $p = .27$). BMI fell significantly in all three groups ($p < .001$, $p < .05$, $p < .001$, respectively).
Vincentelli et al.[29]	39 women (PCOS = 6) underwent sleeve gastrectomy or Roux-en-Y gastric bypass surgery	AMH levels significantly decreased at 6 and 12 months post-operatively ($p = .010$ and $p = .001$) for both procedures with mean excess weight loss 61.7% at 6 months and 70.2% at 12 months.

current findings. As for surgical weight loss, Chiofalo et al. followed 26 women with obesity without PCOS and 29 women with obesity with PCOS who underwent bariatric surgery. Mean weight loss was 65% ± 19% of starting weight for both groups after 1 year. AMH decreased by an average of 26% ($p = .04$) in the non-PCOS group and by 22% ($p = .02$) in the PCOS group.[16] Similarly, Vincentelli et al. published a study in 2018 including 39 women with obesity who underwent bariatric surgery, six of whom had PCOS. Overall, AMH levels decreased by an average of 18% at 6 months and 35% at 12 months post-surgical intervention ($p = .01$, $p = .001$, respectively). A significant decrease was also reported specifically in the cohort without PCOS at 6- and 12-months postoperatively ($p = .002$). There was no relationship between fat-mass loss and AMH decrease.[29] Bhandari et al. also reported a drop in AMH in 75 patients with and without PCOS after surgery.[17] Merhi et al. only reported a change in its cohort of women under 35 years of age. In this group of seven women, AMH levels decreased significantly after bariatric surgery.[30] However, Milone et al. opposed these findings, reporting no post-operative change within its group of 40 patients.[31] Nilsson-Condori et al. observed a negative change in AMH levels after surgical weight-loss. However, this group of 48 women, most without PCOS, underwent 8 weeks of calorie restriction prior to gastric bypass, during which a significant rise in AMH was noted.[32] In contrast, caloric restriction or nutritious diets in patients with PCOS have been found to decrease AMH in several studies.[33,34] The impact of exercise has also been assessed with varying results in two small studies, one totalling 15 women and another totalling 57, with differing results between the two.[33,35]

4 | DISCUSSION

Today, over one-third of the world's population has overweight or obesity.[36] In addition to increased post-pregnancy complications, elevated BMI is associated with reduced fertility as well as higher rates of miscarriage and pregnancy complications.[37] Women with

overweight and obesity have been shown to have increased time-to-pregnancy.[38] This estimation of fecundity remains abnormal even among women with overweight and obesity with regular menstrual cycles.[39] Success of assisted reproductive technology is negatively correlated with BMI; Pinborg et al. found the rate of pregnancy per IVF cycle was lower in women with obesity. Results also revealed that as BMI increased, the number of IVF cycles per patient did as well, while the number of retrieved oocytes declined.[40] Reduced oocyte quality and implantation rates are also described as factors in reduced fertility among patients with high BMIs. Reproductive-aged female patients with obesity may be referred to or seek medical weight loss management, including bariatric surgery, which can improve physiologic ovulation and menstrual cycles.[41]

4.1 | AMH and BMI

Despite the well-documented detriment of obesity on fertility and the common use of AMH as a fertility marker, there is no consensus as to whether BMI affects AMH. Although PCOS is known to be associated with increased AMH levels, both PCOS and non-PCOS populations have been found to have contradictory results when considering the association of BMI and AMH. The majority of the literature reports either a negative correlation or none at all. Two studies found a positive correlation, but these findings were not demonstrated above BMIs of 25 kg/m^2 and are presently outnumbered by literature evidencing negative correlations.

Several limitations exist in the current literature that may hinder our true understanding of the issue or contribute to the contradictory findings. First, many studies group all obese BMIs into one cohort, and several of these reported an association between BMI and AMH only within their cohorts without overweight or obesity.[18,19,21] However, Bernardi et al.'s further stratification of BMI revealed a negative relationship in BMIs above 40 kg/m^2.[20] Although finding no association in either their PCOS and non-PCOS cohorts, Bhandari et al. did report that in a mixed PCOS-status cohort with BMIs above 51 kg/m^2, AMH levels declined significantly.[17] These results suggest it may be important to analyse BMIs with more granularity beyond the broad definitions of normal weight, overweight and obesity determined by the World Health Organization (WHO). Additionally, many of the mean BMIs of the cohorts with obesity trend toward the low end of the WHO definition (Tables 1 and 2), limiting insight across the full spectrum of obesity.

This review also indicates that race/ethnicity and duration of obesity may influence AMH levels and are variables of specific interest in future research. Still, the data is contradictory: Moy et al. found a significant relationship only in the Caucasian cohort; however, compared with the African American, Asian American and Hispanic cohorts, the Caucasian group had the largest sample size and lowest mean BMI.[22] If a relationship between BMI and AMH exists only at lower BMIs, as proposed by several studies,[18,21] Moy et al.'s findings between cohorts may be a result of differences in BMI as opposed to race/ethnicity. However, Shaw et al.'s study of Caucasian women demonstrated no correlation between AMH and BMI.[14] This group of women had a mean BMI nearly identical to the Caucasian group in Moy et al., while the former found no relationship and the latter found a negative one. Thus, in this case, neither BMI nor race/ethnicity can explain the different results.

In addition to race/ethnicity, other variables that have been postulated to influence AMH and may be worthy of future review include smoking and oral contraceptive use.[14,21] For example, Shaw et al. determined AMH levels differed significantly between those who do and do not use oral contraceptives.[14] However, these variables were not consistently controlled for between the included studies, possibly contributing to the conflicting results. Any future research performed prior to a consensus regarding these potential confounders should control for them to ensure validity.

Furthermore, while we used the language of the primary literature in describing potential differences between races/ethnicities, we recognize that any differences found between these groups may not be a result of race/ethnicity itself, but rather due to confounding variables as they relate to shared culture. Additional studies would need to distinguish the contributions of biology and behaviour.

4.2 | AMH and weight loss

Similarly incompatible results have been shown in weight-loss studies. Of the six studies analysing the effect of bariatric surgery, five found evidence of falling AMH levels within at least one cohort. Milone et al. disagreed with these findings, instead reporting no significant change after surgery; however, the study population consisted exclusively of women with a history of assisted reproductive technology failure and idiopathic infertility, a characteristic that should not be overlooked as a potential influence.[31] Merhi et al. reported no change in its population of women over 35 years of age, but this constituted only 9 women, the smallest sample size of any of the included bariatric surgery studies.[30] As such, most current evidence within 1 year post-operatively indicates a negative association between bariatric surgery and AMH levels. Declining AMH levels were also found in several studies of diet or exercise,[33,34] but Nilsson-Condori et al. and Al-Eisa et al. reported an increase in AMH as a result of such non-surgical interventions.[32,42] However, the three small studies reporting on food-based interventions, which showed conflicting results, did not share a common diet; instead, some focused on strictly limiting total calories, while others focused on providing nutritious foods. Similarly, exercise protocols were not standardized between studies, varying in their total time course and intensity, as well as in their results. Nybacka et al., who found that physical training did not influence AMH levels, stated that they could not explain their difference in results from Moran et al., but noted Moran et al. utilized a more rigorous exercise program.[33,35] As a result of the heterogeneity between studies, it is difficult to know whether the impact of weight loss on AMH is merely the result of a change in adiposity, or instead influenced by how that change is achieved. Furthermore, several weight

loss studies did not analyse cohorts with and without PCOS separately which may obscure differences between the two groups. As PCOS increases baseline AMH levels, it may be necessary to investigate changes in AMH after weight loss differently between patients with and without the diagnosis. One study found that PCOS status determined whether AMH changed in response to exercise, supporting a need for separate analyses.[35]

Thus, although most data presently suggests that bariatric surgery is associated with a post-operative decrease in AMH levels, this data is limited, both in the number of reports addressing this question and the number of participants included within them. Studies assessing non-surgical weight loss are even more scarce and difficult to analyse due to exceptionally small sample sizes and their use of significantly different methods. Replicating the current studies with appropriate power and control of potentially confounding variables would shine a light on their validity and facilitate their proper interpretation.

4.3 | Proposed mechanisms

Several mechanisms have been proposed supporting a negative relationship between BMI and AMH levels. Adipocytes are lipid-storing cells that are the main component of adipose tissue. These cells produce leptin, a hormone known for its inhibition of hunger. Leptin has been shown to suppress secretion of AMH from granulosa cells in in-vitro studies.[43] A negative relationship between leptin and AMH was demonstrated by Bernardi et al. where increased adiposity was associated with higher leptin levels and lower AMH levels.[20]

Insulin resistance may also play a role in AMH secretion, as hyperinsulinemia may induce premature differentiation of granulosa cells.[44] Sahmay et al., however, found no difference in AMH levels in women with and without insulin resistance.[24] It is also possible that gonadotropin-releasing hormone (GnRH) is a mediator in the negative relationship between insulin and AMH. Hyperinsulinemia may induce GnRH secretion,[45,46] and GnRH has been shown to reduce AMH levels.[47] Still, the relationship between insulin resistance and GnRH dysregulation has not been fully elucidated, and the relevance of findings from mouse models to humans is uncertain.[45,46]

Women with obesity may also have decreased levels of adiponectin,[48] a hormone secreted from adipose tissue involved in glucose regulation and fatty acid oxidation. This mechanism could involve adiponectin's role as an insulin-sensitizer, harking back to the proposed role of insulin resistance and AMH. Dysfunctional folliculogenesis and reduced AMH expression may also be due to adiponectin's negative regulation of aromatase, the enzyme that converts androgens to estrogens, leading to alternated aromatization.[49]

Weight loss results in a decrease in oestrogen, leptin, insulin and an increase in adiponectin.[50] Oestrogen does not appear to modulate AMH secretion.[51] If adiponectin or insulin resistance do modulate AMH secretion, then given the theories described above, one would expect AMH levels to rise with weight loss, a finding that was not observed in the referenced studies on weight-loss surgery. Thus, these mechanisms may not entirely explain the relationship between BMI and AMH. Further, leptin levels have been found to decrease after bariatric surgery and these levels are strongly correlated with BMI at 1-year post-operation.[52] Leptin may suppress AMH mRNA, as mentioned above and as shown by Merhi et al. via the JAK2/STAT3 pathway.[43] Again, contrary to the literature, this creates the expectation that AMH levels will increase after bariatric surgery, suggesting there may be another mechanism by which weight loss decreases AMH. It is possible that a decline in AMH levels due to weight loss is specifically the result of bariatric surgery itself rather than decreased adiposity. This would make sense of the data suggesting an AMH fall with surgery, but not an AMH rise with BMI. Further supporting this are Nilsson-Condori et al.'s study in which non-surgical, caloric restriction weight loss produced an increase in AMH and Vincentelli et al.'s report that the significant post-surgical drop in AMH levels had no relationship to fat-mass lost.[29,32] Merhi et al. suggested that surgical weight loss may result in malabsorption of substances that affect AMH gene expression.[30] It is also possible that the speed at which adiposity changes after bariatric surgery is a factor: Vincentelli et al. offered for consideration that endocrine disruptors in adipose tissue may be released during rapid weight loss, impairing AMH secretion by granulosa cells.[29]

5 | CONCLUSION

As markers of ovarian reserve are used to predict the value of therapies such as controlled ovarian hyperstimulation, the utility of AMH as a marker of ovarian reserve or response in women with obesity is uncertain. This uncertainty stems from the mixed results regarding the AMH and BMI relationship, as well as what a potential negative relationship could represent, whether it be truly diminished ovarian reserve or AMH as a poor proxy in populations with obesity. Our results underscore the importance of a more detailed analysis beyond the current, broad classes of body mass, as well as one that encompasses the full range of obesity. Future studies will require appropriate design and sample size calculations to adequately address this question.

AUTHOR CONTRIBUTIONS

Jacqueline Kloos was responsible for designing the literature review, conducting the search, screening potentially eligible studies, extracting data, interpreting results and drafting the manuscript. Kathryn Coyne contributed to writing the manuscript and interpreting results. Rachel Weinerman contributed to the design of the literature review and interpretation of the results. All authors provided critical review and revisions of the manuscript.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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