Obesity on Anti-Mullerian Hormone Levels

Subjects: Others

Contributor: Alexis Oldfield

Some women with obesity have regular cycles, yet their reproductive hormone profile suggests some level of ovarian dysfunction that could manifest as disordered AMH production compared to their lean counterparts. Differences in AMH production across the adiposity spectrum could lead to inaccurate conclusions about the ability of AMH to adequately inform reproductive health outcomes in women. To address the current knowledge gap, we conducted a review to provide an up-to-date account of AMH levels in obese and non-obese women with regular menstrual cycles with the goal of establishing the degree to which obesity impacts AMH production in healthy, potentially fertile women.

Keywords: obesity ; Anti-Müllerian hormone ; ovary ; body mass index ; menstrual cycle

1. Introduction

Obesity remains a persistent and growing public health concern, with current rates nearing 40% of reproductive-aged women in the United States [1]. Obesity impacts a broad array of health risks in women across the lifespan [2], including adverse reproductive health outcomes such as menstrual cycle irregularity, abnormal uterine bleeding, endometrial hyperplasia, infertility, and pregnancy complications [3][4][5][6][7]. Furthermore, women with obesity are 20% more likely to experience later onset of menopause, which in part may underlie the increased risk of breast, ovarian, and uterine cancer seen in this population [8]. While the impact of obesity on reproductive health is known to be multi-factorial, many of the adverse reproductive outcomes may be linked to endocrine disruptions that reflect an impaired ovarian function [9]. Specifically, infertility observed in women with obesity is commonly associated with ovulatory disturbances and irregular menstrual cyclicity [10]. However, even women with obesity and regular menstrual cycles exhibit a longer time to spontaneous pregnancy [11][12][13][14] and lower success rates of controlled ovarian hyperstimulation compared to their normal-weight counterparts [15]. This potential for subfertility aligns with previous reports of an altered reproductive hormone profile in women with obesity and regular cycles including, decreased follicle stimulating hormone (FSH) levels [16], decreased luteinizing hormone (LH) pulse amplitude [17], increased estradiol levels [16], and decreased luteal phase progesterone production [17]. Despite strides toward characterizing the nature of reproductive disturbances in obesity, several questions remain to be answered on how and why obesity may drive disordered ovarian function.

To that end, an altered ovarian follicular environment has been confirmed in women with obesity and involves disruptions in multiple systems, including steroidogenic action, metabolism, and inflammation, all of which can impact folliculogenesis and ovulatory potential [18]. The degree to which obesity impacts ovarian reserve is more controversial as available data have largely focused on sub- or infertile populations, wherein studies have not shown consistent associations between serum markers of ovarian reserve and body mass index (BMI) [4][19]. Anti-Mullerian hormone (AMH), a glycoprotein primarily produced by the granulosa cells of primary and early-stage antral follicles, is a marker whose association with obesity is controversial [20][21][22]—albeit a single meta-analysis suggests a negative association of AMH with BMI [19]. A growing interest in the use of AMH to predict reproductive health outcomes related to response to controlled ovarian stimulation [23], diagnosis of ovulatory disorders [24], the onset of menopause [25], and even natural conception [26] necessitate an understanding of biological factors, such as obesity, that could impact the predictive power of AMH for such reproductive outcomes.

The mechanisms through which obesity may adversely affect AMH production are unknown, but it has also been shown that with increasing adiposity, AMH production per antral follicle is reduced [27]. One possibility relates to an altered metabolic regulation of ovarian granulosa cells. Obesity is commonly associated with systemic insulin resistance and compensatory hyperinsulinemia. Excessive insulin levels have been shown to alter granulosa cell receptivity, and subsequently, AMH production [28]. Likewise, the increased leptin production associated with obesity could directly suppress AMH production. This observation is derived from the inhibitory effects of leptin administration on AMH and AMH receptor gene expression in cultured granulosa cells from patients undergoing controlled ovarian hyperstimulation [29]. More indirect in nature is the notion that lower AMH levels in women with obesity may result from a hemodilution effect of increasing body size [27]. Another possibility includes an impact of obesity on AMH catabolism and excretion. Obesity is

known to alter the excretion of other reproductive hormones such as FSH, estradiol, and progesterone [17]. However, the exact mechanisms of AMH excretion are unknown [30]. Last, obesity may have an increased apoptotic effect at the ovarian follicle level, which is a mechanism observed in animal models [31]. While this posited mechanism may explain a reduced ovarian follicle pool and AMH levels, it seems less likely based on existing data of a later time to ovarian senescence in women with obesity.

Our current demographic necessitates further consideration of the impact of obesity on AMH production in healthy women of reproductive age. Most of the available data on AMH levels have been focused on women with infertility and/or polycystic ovary syndrome (PCOS) [32][33]. Of the data available in otherwise healthy women, AMH levels have been more commonly reported in women of lean BMI or women of advanced reproductive age [34][35]. Some women with obesity have regular cycles, yet their reproductive hormone profile suggests some level of ovarian dysfunction that could manifest as disordered AMH production compared to their lean counterparts [11]. Differences in AMH production across the adiposity spectrum could lead to inaccurate conclusions about the ability of AMH to adequately inform reproductive health outcomes in women. To address the current knowledge gap, we conducted a review to provide an up-to-date account of AMH levels in obese and non-obese women with regular menstrual cycles with the goal of establishing the degree to which obesity impacts AMH production in healthy, potentially fertile women.

2. Methods

This work represents a narrative review. The methods have been summarized herein.

Our primary outcome was serum AMH levels.

A search of published literature was conducted in the electronic databases of MEDLINE (PubMed), Institute for Scientific Information (ISI) Web of Science, and Scopus through 27 July 2020, using a search strategy based on the PEO framework, as described above. In short, studies included for review were limited to original research articles in which (1) the study was conducted in healthy, reproductive-aged (18–48 years) regularly cycling women, (2) the exposure was obesity, and (3) AMH levels were reported as an outcome for non-obese and obese groups. Only articles published in English were included. Studies must have used BMI as a categorical term, with obesity defined as a BMI > 30 kg/m 2 and non-obese defined as some value < 30 kg/m 2. Where AMH levels were reported separately for overweight women (BMI > 25 and <30 kg/m 2), data were pooled with non-obese women where possible. Every record retrieved by this search strategy underwent a title and abstract screening to confirm that it aligned with the inclusion criteria. Articles that were relevant and appropriate were downloaded for full-text review, and data on the general characteristics of the study, patient population, study design, obesity definitions, AMH levels, and inclusion and exclusion criteria were extracted.

Briefly, observational (cross-sectional, case-control, cohort) studies or cross-sectional analysis of baseline measures from randomized controlled trials on women with regular menstrual cycles were included wherein the influence of obesity (non-obese and obese subtypes) as an exposure variable was evaluated on our study outcomes of interest. Non-peer-reviewed studies; studies without the design of interest; studies wherein our outcomes of interest were not compared between non-obese and obese women with regular cycles; studies that were not conducted on healthy women; studies in women with PCOS and women who had single isolated features of PCOS (hyperandrogenism, oligo- or amenorrhea, and polycystic ovarian morphology); studies featuring children (<17 years), pregnant women, or menopausal-aged women (>48 years); and, where study data were irretrievable after contacting their corresponding authors were excluded.

3. Findings

Of the 13 studies identified in this review, eight involving a total of 193 obese and 261 non-obese women with regular menstrual cycles documented no significant differences in AMH levels between groups. Percent differences in AMH levels between groups ranged from −70.4% to 62.5% (Mean: −5.5%; Median: 2.5%). BMI of the non-obese participants ranged from 21.6 to 25.6 kg/m 2, and BMI of the obese participants ranged from 31.7 to 34.3 kg/m 2, which is consistent with the inclusion of women with strictly Class 1 (30 to <35 kg/m 2) obesity. Studies were conducted across a broad array of countries and included diverse ethnic populations from North America [36][37], South America [38], Asia [39][40][41], and Africa [42][43]. Participants ranged in age from 23.8 to 46.2 years, with the mean age across studies being approximately 29 years. Studies were largely cross-sectional in nature and involved an assessment of serum AMH levels at a single time point during the menstrual cycle. The timing of the AMH assessment was not standardized to a particular stage of the cycle for all studies, however, six [38][40][43][44][45][46][47] of the 13 studies did measure AMH during the early follicular phase, (days 2–7). According to the most recent position statement by the American Society for Reproductive Medicine (ASRM), intracycle variation in AMH is considered minimal, and standardizing the timing of assessments is not a requirement at this time [48].

References

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Five out of thirteen studies involving 210 obese and 550 non-obese women with regular menstrual cycles documented either significantly lower AMH levels in the obese compared to non-obese groups and/or a negative association between AMH and BMI. Percent differences in AMH levels between groups ranged from −9.7% to −76.7% (Mean: −27.4%; Median: −21.8%). The BMI of the non-obese participants ranged from 20.7 to 22.4 kg/m 2, and that of the obese participants ranged from 33.0 to 46.0 kg/m 2, which is consistent with the inclusion of women across Class 1 (30 to <35 kg/m 2), Class 2 (35 to <40 kg/m 2), and Class 3 (40 kg/m 2 or higher) obesity—as well as a lack of any overweight individuals in the non-obese group. Studies were also conducted across a broad array of countries and included diverse ethnic populations from North America [46][47] and Europe [44][45][49]. Participants ranged in age from 23 to 46 years, with the mean age across studies being approximately 30 years. Studies were largely cross-sectional in nature and involved an assessment of serum AMH levels at a single time point during the menstrual cycle. Collectively, this group of studies included a similar number of obese women but more than double the number of non-obese women compared to the studies that reported no difference in AMH across BMI groups. A broader range of obesity was represented, but studies were more limited in their geographic representation. jcm-10-03192-t001_Table 1 **Table 1** Characteristics of studies reporting AMH levels in non-obese and obese reproductive-aged women with regular menstrual cycles. Lead Author, Publication Year (Country) Participants' Characteristics (n, Age (Year), BMI (kg/m 2)) Group Definitions Based on BMI (kg/m 2) Study Design Assay Type, Method Cycle Day or Stage AMH Levels Correlation (p -Value) Adjustment for Confounders Exclusion Criteria Obese Non-Obese p -Value across BMI Groups * Al-Eisa 2017 (Egypt) [43] Non-obese group (n , 30; age, 28.7; BMI, 22.8) Obese group (n , 30; age, 27.6; BMI, 31.7) Non-obese: 20–29 Obese: 30–35 Cross- sectional analysis of a non-randomized trial Beckman Coulter ELISA Day 2–3 4.60 (3.11–6.09) 2.83 (0.03–5.63) >0.05 NR Any PCOS feature, infertility, concomitant diseases, ovarian issues, use of drugs that affect hormone levels Chiofalo 2017 (Italy) [49] Non-obese group (n , 19; age, 30; BMI, 22) Obese group (n , 26; age, 33; BMI, 46) Non-obese: <25 Obese: >30 Cohort Gen II Beckman Coulter ELISA Random 2.14 (0.81–3.47) 2.37 (0.17–4.57) <0.0001 NR PCOS, use of estroprogestin, metformin or inositol, hyperprolactinemia, and endocrine disorders Eken 2019 (Turkey) [39] Non-obese group (n , 38; age, 26.66; BMI, NR) Obese group (n , 31; age, 26.03; BMI, NR) Non-obese: 18.5–24.9 Obese: >30 Cross- sectional Ansh Labs AMH ELISA Early follicular phase 2.56 (1.78–3.34) 2.30 (1.58–3.02) >0.05 NR PCOS, androgen-producing tumors, 21-hydroxylase deficiency, adrenal hyperplasia, hyperprolactinemia, thyroid disease, Cushing's, smoking, and use of insulin sensitizers and/or medications that interfere with reproduction Ersoy 2017 (Turkey) [41] Non-obese group (n , 36; age, 26.4; BMI, 21.6) Obese group (n , 26; age, 26.7; BMI, 32.8) Non-obese: 18.5–24.9 Obese: >30 Cross- sectional Ansh Labs AMH ELISA Day 2–4 3.10 (2.10–4.10) 3.10 (2.10–4.10) NR NR PCOS, diabetes, Cushing's, adrenal hyperplasia, androgen-secreting tumors, thyroid dysfunction, hyperandrogenism, hormonal drug use, and smoking, alcohol abuse Halawaty 2010 (Egypt) [42] Non-obese group (n , 50; age, 46.1; BMI, 25.6) Obese group (n , 50; age, 46.2; BMI, 32.9) Non-obese: <30 Obese: 30–35 Prospective DSL AMH ELISA Day 2–5 2.55 (1.74–3.36) 3.39 (3.15–3.63) 0.56 NR Use of hormones, smoking, pregnancy, lactation, hysterectomy, previous ovarian surgery, any PCOS feature, endometriosis, and other medical conditions that could affect ovarian function Olszanecka-Glinianowicz, 2015 (Poland) [45] Non-PCOS group (n , 36/67 obese; age, NR; BMI, NR) Non-obese: 18.5–24.9 Obese: >30 Observational Immunotech ELISA Day 3–5 3.90 (1.60–6.20) 5.10 (2.70–7.50) <0.05 −0.075 (p < 0.05) Age Hyperandrogenism, PCOS, infertility, smoking, and alcohol use Peigne 2020 (France) [44] Non-obese group (n , 21; age, 32.0; BMI, 20.7) Obese group (n , 16; age, 31.5; BMI, 33.7) Non-obese: <25 Obese: >30 Case-Control DXI sandwich chemiluminescent immunoassay Early follicular phase 0.87 API: 34.6% 0.92 API: 39.02% p > 0.05 p < 0.001 NR API −0.557 (p < 0.01) Any PCOS feature, use of medications that affect metabolism or ovarian function within 3 months Roth 2014 (United States) [37] Non-obese group (n , 10; age, 27.3; BMI, 22.3) Obese group (n , 10; age, 32.5; BMI, 34.3) Non-obese: 18.5–25 Obese: >30 Cross- sectional Gen II Beckman Coulter ELISA Mid-cycle 0.02 (0.01–0.06) 0.05 (0.02–0.10) 0.10 NR Hyperandrogenism, chronic diseases, use of exogenous sex steroids or medications known to affect reproductive hormones, regular exercise >4 h weekly, or attempting pregnancy Shahin 2020 (Jordan) [40] Non-obese group (NR) Obese group (NR) Non-obese: 18.5–25 Obese: >30 Case-Control Roche Cobas ECLIA Day 2–4 3.11 (0.92–5.3) 2.91 (−0.16–5.98) 0.70 NR PCOS, congenital adrenal hyperplasia, Cushing's, malabsorptive or eating disorders, menopause, history of bariatric surgery Shaw 2011 (United States) [36] Non-obese group (n , 31; age, 23.8; BMI, 22.2) Obese group (n , 36; age, 27.3; BMI, 33.4) Non-obese: <25 Obese: >30 Case-Control Beckman Coulter ELISA Random 0.64 0.61 0.76 NR Post-menopause, breast cancer Steiner 2017 (United States) [46] Non-obese group (n , 461; age, NR; BMI, NR) Obese group (n ,114; age, NR; BMI, NR) Non-obese: 18.5–24.9 Obese: >30 Cohort Gen II Beckman Coulter ELISA Day 2–4 2.20 (0.90–4.00) 2.85 (1.50–5.50) 0.06 NR Known fertility problems (sterilization, PCOS, tubal blockage), endometriosis, previous or current use of fertility treatments, partner with a history of infertility, lactation, recent use of injectable hormonal contraception Su 2008 (United States) [47] Non-obese group (n , 18; age, 45; BMI, 22.4) Obese group (n , 18; age, 45.1; BMI, 37.6) Non-obese: <25 Obese: >30 Cross- sectional DSL AMH ELISA Day 1–4 0.07 (0.03–0.15) 0.30 (0.14–0.63) 0.01 p = 0.02 Hormonal therapy, contraception, PCOS Woloszynek 2015 (Brazil) [38] Non-obese group (n , 66; age, NR; BMI, NR) Obese group (n , 10; age, NR; BMI, NR) Non-obese: <25 Obese: >30 Cross-sectional Gen II Beckman Coulter ELISA Day 2–7 1.90 (0.40–10.90) 2.90 (0.30–11.20) 0.29 NR Chronic diseases, menstrual irregularity, PCOS, infertility, hysterectomy,

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oophorectomy, serum LH and FSH concentrations out of the reference ranges PCOS, polycystic ovary syndrome; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; NR, not reported; OCP, oral contraceptive pill; LH, luteinizing hormone; FSH, follicle-stimulating hormone, ECLIA, electrochemiluminescence immunoassay; API, AMH; prohormone index ; AMH levels expressed as ng/mL. Mean (±SD) or Median (25–75th) are presented as provided by the manuscript. * Spearman's correlation is presented where available.

Table 1. Characteristics of studies reporting AMH levels in non-obese and obese reproductive-aged women with regular menstrual cycles.

Lead Author, Publication Year (Country)	Participants' Characteristics (n, Age (Year), BMI (kg/m²))	Group Definitions Based on BMI (kg/m²)	Study Design	Assay Type Method	Cycle Day or Stage	AMH Levels Obese	AMH Levels Non-Obese	p-Value across BMI Groups *	Correlation (p-Value) Adjustment for Confounders	Exclusion Criteria
Al-Eisa 2017 (Egypt) [43]	Non-obese group (n, 30; age, 28.7; BMI, 22.8) Obese group (n, 30; age, 27.6; BMI, 31.7)	Non-obese: 20–29 Obese: 30–35	Cross-sectional analysis of a non-randomized trial	Beckman Coulter ELISA	Day 2–8	4.60 (3.11–6.09)	2.83 (0.03–5.63)	>0.05	NR	Any PCOS feature, infertility, concomitant diseases, ovarian issues, use of drugs that affect hormone levels
Chiofalo 2017 (Italy) [49]	Non-obese group (n, 19; age, 30; BMI, 22) Obese group (n, 26; age, 33; BMI, 40)	Non-obese: <25 Obese: >30	Cohort	Gen II Beckman Coulter ELISA	Random	2.14 (0.81–3.47)	2.37 (0.17–4.57)	<0.0001	NR	PCOS, use of estroprogestin, metformin or inositol, hyperprolactinemia, and endocrine disorders
Eken 2019 (Turkey) [39]	Non-obese group (n, 38; age, 26.66; BMI, NR) Obese group (n, 31; age, 26.03; BMI, NR)	Non-obese: 18.5–24.9 Obese: >30	Cross-sectional	Ansh Labs AMH ELISA	Early follicular phase	2.56 (1.78–3.34)	2.30 (1.58–3.02)	>0.05	NR	PCOS, androgen-producing tumors, 21-hydroxylase deficiency, adrenal hyperplasia, hyperprolactinemia, thyroid disease, Cushing's, smoking, and use of insulin sensitizers and/or medications that interfere with reproduction
Ersoy 2017 (Turkey) [41]	Non-obese group (n, 36; age, 26.4; BMI, 21.6) Obese group (n, 26; age, 26.7; BMI, 32.8)	Non-obese: 18.5–24.9 Obese: >30	Cross-sectional	Ansh Labs AMH ELISA	Day 2–4	3.10 (2.10–4.10)	3.10 (2.10–4.10)	NR	NR	PCOS, diabetes, Cushing's, adrenal hyperplasia, androgen-secreting tumors, thyroid dysfunction, hyperandrogenism, hormonal drug use, and smoking, alcohol abuse
Halawaty 2010 (Egypt) [42]	Non-obese group (n, 50; age, 46.1; BMI, 26.6) Obese group (n, 50; age, 46.2; BMI, 32.9)	Non-obese: <30 Obese: 30–35	Prospective	DSL AMH ELISA	Day 2–5	2.55 (1.74–3.36)	3.39 (3.15–3.63)	0.56	NR	Use of hormones, smoking, pregnancy, lactation, hysterectomy, previous ovarian surgery, any PCOS feature, endometriosis, and other medical conditions that could affect ovarian function

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Lead Author, Publication Year (Country)	Participants' Characteristics (n, Age (Year), BMI (kg/m²))	Group Definitions Based on BMI (kg/m²)	Study Design	Assay Type, Method	Cycle Day or Stage	AMH Levels		p-Value across BMI Groups	Correlation (p-Value) Adjustment for Confounders	Exclusion Criteria
						Obese	Non-Obese			
Olszanecka-Glinianowicz, 2015 (Poland) [45]	Non-PCOS group (*n*, 36/67 obese; age, NR; BMI, NR)	Non-obese: 18.5–24.9 Obese: >30	Observational	Immunotech ELISA	Day 3–5	3.90 (1.60–6.20)	5.10 (2.70–7.50)	<0.05	−0.075 ($p < 0.05$) Age	Hyperandrogenism, PCOS, infertility, smoking, and alcohol use
Peigne 2020 (France) [44]	Non-obese group (*n*, 21; age, 32.0; BMI, 20.7) Obese group (*n*, 16; age, 31.5; BMI, 33.7)	Non-obese: <25 Obese: >30	Case-Control	DXI sandwich chemiluminescent immunoassay	Early follicular phase	0.87 API: 34.6%	0.92 API: 39.02%	$p > 0.05$ $p < 0.001$	NR API −0.557 ($p < 0.01$)	Any PCOS feature, use of medications that affect metabolism or ovarian function within 3 months
Roth 2014 (United States) [37]	Non-obese group (*n*, 10; age, 27.3; BMI, 22.3) Obese group (*n*, 10; age, 32.5; BMI, 34.3)	Non-obese: 18.5–25 Obese: >30	Cross-sectional	Gen II Beckman Coulter ELISA	Mid-cycle	0.02 (0.01–0.06)	0.05 (0.02–0.10)	0.10	NR	Hyperandrogenism, chronic diseases, use of exogenous sex steroids or medications known to affect reproductive hormones, regular exercise >4 h weekly, or attempting pregnancy
Shahin 2020 (Jordan) [40]	Non-obese group (NR) Obese group (NR)	Non-obese: 18.5–25 Obese: >30	Case-Control	Roche Cobas ECLIA	Day 2–4	3.11 (0.92–5.3)	2.91 (−0.16–5.98)	0.70	NR	PCOS, congenital adrenal hyperplasia, Cushing's, malabsorptive or eating disorders, menopause, history of bariatric surgery
Shaw 2011 (United States) [36]	Non-obese group (*n*, 31; age, 23.8; BMI, 22.2) Obese group (*n*, 36; age, 27.3; BMI, 33.4)	Non-obese: <25 Obese: >30	Case-Control	Beckman Coulter ELISA	Random	0.64	0.61	0.76	NR	Post-menopause, breast cancer
Steiner 2017 (United States) [46]	Non-obese group (*n*, 461; age, NR; BMI, NR) Obese group (*n*,114; age, NR; BMI, NR)	Non-obese: 18.5–24.9 Obese: >30	Cohort	Gen II Beckman Coulter ELISA	Day 2–4	2.20 (0.90–4.00)	2.85 (1.50–5.50)	0.06	NR	Known fertility problems (sterilization, PCOS, tubal blockage), endometriosis, previous or current use of fertility treatments, partner with a history of infertility, lactation, recent use of injectable hormonal contraception
Su 2008 (United States) [47]	Non-obese group (*n*, 18; age, 45; BMI, 22.4) Obese group (*n*, 18; age, 45.1; BMI, 37.6)	Non-obese: <25 Obese: >30	Cross-sectional	DSL AMH ELISA	Day 1–4	0.07 (0.03–0.15)	0.30 (0.14–0.63)	0.01	$p = 0.02$	Hormonal therapy, contraception, PCOS

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Lead Author, Publication Year (Country)	Participants' Characteristics (n, Age (Year), BMI (kg/m^2))	Group Definitions Based on BMI (kg/m^2)	Study Design	Assay Type, Method	Cycle Day or Stage	AMH Levels		*p*-Value across BMI Groups *	Correlation (*p*-Value) Adjustment for Confounders	Exclusion Criteria
						Obese	Non-Obese			
Woloszynek 2015 (Brazil) [38]	Non-obese group (*n*, 66; age, NR; BMI, NR) Obese group (*n*,10; age, NR; BMI, NR)	Non-obese: <25 Obese: >30	Cross-sectional	Gen II Beckman Coulter ELISA	Day 2–7	1.90 (0.40–10.90)	2.90 (0.30–11.20)	0.29	NR	Chronic diseases, menstrual irregularity, PCOS, infertility, hysterectomy, oophorectomy, serum LH and FSH concentrations out of the reference ranges

PCOS, polycystic ovary syndrome; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; NR, not reported; OCP, oral contraceptive pill; LH, luteinizing hormone; FSH, follicle-stimulating hormone. ECLIA; electrochemiluminescence immunoassay; API, AMH; prohormone index; AMH levels expressed as ng/mL. Mean (±SD) or Median (25–75th) are presented as provided by the manuscript. * Spearman's correlation is presented where available.

Characteristics of studies reporting AMH levels in non-obese and obese reproductive-aged women with regular menstrual cycles.

PCOS, polycystic ovary syndrome; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; NR, not reported; OCP, oral contraceptive pill; LH, luteinizing hormone; FSH, follicle-stimulating hormone. ECLIA; electrochemiluminescence immunoassay; API, AMH; prohormone index ; AMH levels expressed as ng/mL. Mean (±SD) or Median (25–75th) are presented as provided by the manuscript. * Spearman's correlation is presented where available.

4. Discussion

Included in this group of eight studies was the lone study whose primary aim was to evaluate differences in AMH levels between obese (n = 50) and non-obese (n = 50) groups. Mean AMH levels were 32.9% lower in the obese group compared to the non-obese group, but differences did not reach statistical significance [42]. While this study used stringent criteria to corroborate the healthy reproductive status of the participants, Halawaty et al. used a narrow definition for obesity (30–35 kg/m 2), which primarily included women with Class 1 obesity. Furthermore, the mean and range of the BMI of the non-obese group were 25.6 and 24–29 kg/m 2, respectively, possibly indicating a small number of women with BMI 18.5–24.9 kg/m 2 in the lean group. Ultimately, the spectrum of adiposity in the study by Halawaty et al. may not have been sufficient to capture a significant effect of obesity on AMH production [42]. It must also be noted that this study focused on establishing an impact of obesity on the markers of ovarian reserve, specifically in older reproductive-aged women during the early transition phase of the late premenopausal state. As such, all women demonstrated regular menstrual cycle length (22–35 days) but also variability in cycle length by seven days in either direction for at least two cycles. The mean age of the non-obese and obese groups was 46.1 and 46.2 years and may not wholly reflect AMH production in younger women that are well outside the perimenopausal transition.

Except for a single study [48], the remaining four studies included in this group were small, involving ≤50 participants in both non-obese and obese cohorts combined. While women in the obese and non-obese groups across all these studies had comparable age distributions, the BMI classes of the groups were variable, especially in those with obesity, and none of the studies included women who were overweight. Of these, the studies by Chiofalo et al. [49] and Olszanecka-Glinianowicz et al. [45] showed significantly lower AMH levels in obese versus non-obese women, with AMH levels being 9.7% ($p < 0.0001$) and 23.5% ($p < 0.01$) lower, respectively. Furthermore, the study by Olszanecka-Glinianowicz et al. showed a negative correlation between AMH levels and BMI ($r = -0.30$, $p < 0001$). Chiofalo et al. evaluated AMH levels as part of an intervention study involving bariatric surgery. As such, their obese group consisted of women with Class 3 obesity (mean BMI = 46 kg/m 2). In contrast, the study by Olszanecka-Glinianowicz et al. that investigated AMH levels in the context of largely Class 1 obesity. Overall, these results suggest that obesity may have a negative impact on AMH across the obesity spectrum with a dose effect that is not linear.

Furthermore, a small study (n = 36), Su et al. (2008) examined associations between obesity and serum and ultrasound measures of ovarian reserve in women of late reproductive age (mean age: 45 years) who did not use hormonal contraceptives or have PCOS [47]. AMH levels were a striking 76.7% lower in the obese cohort compared to the non-

obese group (p = 0.014). The authors identified BMI as an independent predictor of AMH and concluded that lower AMH levels in obese women of late reproductive age resulted from physiologic processes other than a decreased ovarian reserve.

Of the studies with larger sample sizes, Steiner et al. reported a trend (p = 0.06) toward differences in AMH levels across BMI groups involving a total of 750 women in underweight, lean, overweight, and obese groups [46]. In the case of groups of interest to this review, AMH levels were 29.5% and 28.1% lower in 114 obese women with regular cycles and no history of infertility compared to 461 lean and 155 overweight women with similar reproductive health histories, respectively—which is consistent with AMH levels being quite similar in lean and overweight groups. The study was designed to assess any association between the biomarkers of ovarian reserve and time to natural conception in a group of late reproductive age women (30–44 years) in which rigorous approaches were used to exclude known fertility problems, ovaries disorders, and recent hormonal conception use. Ultimately, Steiner et al. adjusted their time to pregnancy models for AMH by BMI to reflect obesity as an important covariate.