

Impact of psychological stress on ovarian function: Insights, mechanisms and intervention strategies (Review)

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Abstract. Mental stress may lead to ovarian dysfunction. Psychological stress disrupts ovarian function, leading to

adverse *in vitro* fertilization outcomes, premature ovarian insufficiency and decreased ovarian reserve. Furthermore, psychological stress caused by decreased ovarian function and infertility can exacerbate the mental burden. In animals, psychological stress leads to ovarian insufficiency, resulting in irregular estrous cycles and decreased ovarian reserve. The present study summarizes effects of psychogenic stress on ovarian function and the underlying mechanisms, highlighting involvement of the hypothalamic-pituitary-adrenal, sympathetic-adrenal-medullary and hypothalamic-pituitary-ovarian axes, as well as the neuroendocrine-metabolic network. Moreover, the present review outlines psychological intervention and metabolic strategies for improving ovarian function, offering potential new approaches for treating ovarian hypofunction. The present study aims to clarify understanding of psychological stress-induced ovarian dysfunction and propose alternative intervention strategies for ovarian dysfunction and infertility.

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Abbreviations: IVF, *in vitro* fertilization; AFC, antral follicle count; AMH, anti-Müllerian hormone; POI, premature ovarian insufficiency; FHA, functional hypothalamic amenorrhea; PCOS, polycystic ovary syndrome; CUS, chronic unpredictable stress; CRS, chronic restraint stress; T2DM, type 2 diabetes mellitus; NEM, neuroendocrine-metabolic; HPO, hypothalamic-pituitary-ovarian; LH, luteinizing hormone; FSHR, follicle-stimulating hormone receptor; ART, assisted reproductive technology; BDI, Beck Depression Inventory; STAI-T, Spielberger Trait Anxiety Inventory; DOR, diminished ovarian reserve; SAA, salivary α amylase; FST, forced swimming test; SPT, sucrose preference test; GnRH, gonadotropin-releasing hormone; BDNF, brain-derived neurotrophic factor; GDF, growth differentiation factor; ROS, reactive oxygen species; SOD, superoxide dismutase; CRH-R, corticotropin-releasing hormone receptor; HPA, hypothalamic-pituitary-adrenal; GVBD, germinal vesicle breakdown; CCNB1, cyclin B1; SAM, sympathetic-adrenal-medullary; StAR, steroidogenic acute regulatory; ET-1, endothelin-1; TST, tail suspension test; OFT, open field test; LDB, light-dark box; EPM, elevated plus maze; PVN, paraventricular nucleus; AVP, arginine vasopressin; IGF, insulin-like growth factor; RFRP3, RFamide-related peptide-3; KISS, kisspeptin; AGE, advanced glycation end-product; BMI, body mass index; HFD, high-fat diet; SIRT1, sirtuin 1; POF, premature ovarian failure; CBT, cognitive behavioral therapy; AMD, adjusted mean difference; MBSR, mindfulness-based stress reduction; MEC, menopause education control; MRS, Menopause Rating Scale; CCRI, cognitive coping and relaxation intervention; CRM, caloric restriction mimetic

Key words: stress, ovarian function, HPA axis, SAM axis, HPO axis, neuroendocrine-metabolic disease

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1. Introduction

Globally, stress is a prevalent issue. Mental health obstacles, such as social isolation, fear, loneliness, unemployment, financial instability and loss of family or friends, all contribute to psychological stress (1). Mental stress causes physical health problems, including weakened immune function, hypertension, gastrointestinal issues, cardiovascular disease, sleep disturbance and ovarian dysfunction (2,3). Stress has been widely acknowledged as a key factor that impacts the advancement and onset of ovarian damage (2,4). To the best

of our knowledge, however, no consistent conclusions have been drawn on the impact of stress on ovarian function based on epidemiological data, clinical trials and experimental studies (2,4,5).

There is a growing body of evidence indicating that psychological stress leads to ovarian dysfunction (2,6,7). Notably, for patients undergoing *in vitro* fertilization (IVF) treatment, higher anxiety leads to lower clinical pregnancy (8) and fertilization rates (9), decreased embryo quality (10) and fewer oocytes retrieved (11). A prospective study of 274 patients showed that stress reduced the likelihood of conception during the fertile window each day (12) and participation in stress reduction interventions improves IVF outcomes (11). Mental stress can also affect ovarian reserve, leading to decreased levels of antral follicle count (AFC) (13) and anti-Müllerian hormone (AMH) (14). Moreover, mental stress is also involved in an increased risk of premature ovarian insufficiency (POI) (15), functional hypothalamic amenorrhea (FHA) (16) and polycystic ovary syndrome (PCOS) (17). Furthermore, ovarian insufficiency, such as alteration in female sex hormones, also increases the incidence of depression (18). Similarly, ovarian dysfunction is observed in mental stress models; both chronic unpredictable stress (CUS) (19) and chronic restraint stress (CRS) (20) models lead to depression-like behavior and decreased fertility. Stress can also cause general neuroendocrine system changes, which decrease oocyte quality (21). In recent years, there has been a growing recognition that stress is an emerging risk factor for metabolic disorder (22,23). Metabolic disturbances triggered by stress could lead to conditions such as obesity, type 2 diabetes mellitus (T2DM) and ovary damage (2).

The present study aimed to investigate the association between psychological stress and ovarian function based on existing clinical evidence. Research on psychological-associated stress and female reproductive endocrine function from a neuroendocrine-metabolic (NEM) perspective and the underlying molecular mechanisms are summarized. Additionally, strategies to safeguard ovarian function from psychological stress are explored. The present review may provide new perspectives and directions for research and treatment of ovarian dysfunction and infertility.

2. Materials and methods

Search strategy. MEDLINE (clarivate.com.cn/solutions/medline/) was searched for relevant studies published between January 1960 and December 2023 by using title/abstract terms including ‘stress’, ‘psychological stress’, ‘mental stress’, ‘anxiety’, ‘depression’, ‘distress’, ‘cortisol’, ‘alpha amylase’, ‘primary ovarian insufficiency’, ‘Functional hypothalamic amenorrhea’, ‘polycystic ovary syndrome’, ‘IVF’, ‘assisted reproductive technology’, ‘menopause’, ‘ovarian reserve’, ‘anti-Müllerian hormone’, ‘antral follicle count’, ‘Chronic stress’, ‘chronic unpredictable stress’, ‘restraint stress’, ‘chronic restraint stress’, ‘cold stress’, ‘follicles’, ‘oocytes’, ‘granulosa cells’, ‘ovulation’, ‘estrous cycle’, ‘ovarian hormone’, ‘HPA’, ‘SAM’, ‘CRH’, ‘metabolic syndrome’, ‘insulin resistance’, ‘diabetes’, ‘obesity’, ‘sleep disorders’, ‘melatonin’, ‘psychological intervention’, ‘cognitive behavioral therapy’, ‘mindfulness-based stress reduction’,

‘music therapy’, ‘yoga’, ‘caloric restriction’, ‘metformin’, ‘resveratrol’ or in combination, applying AND and OR operators. To obtain more comprehensive retrieval results, the references of relevant papers were also searched.

Inclusion and exclusion criteria. Research and review articles focusing on the role of stress on ovarian function were included. By contrast, research and review articles focusing on the effect of disorders associated with ovarian dysfunction on mental stress, including communications, case reports, guidelines, comments and protocols, were excluded from the present review. Articles written not in English or without available full text were also excluded.

Data extraction. The title and abstract of every article were checked by two authors (YH and WW). Disagreements were resolved by a third author (FF). A total of 7,623 articles were found by the initial search; 7,316 papers were removed after checking the title and abstract. Next, 307 papers were filtered for full text, of which 183 met the inclusion criteria; 36 were population studies on the effect of stress on ovarian function, 71 were animal models and 26 were psychological and 50 were metabolic intervention studies.

3. Stress causes ovarian dysfunction

It has been hypothesized that stress may affect ovarian function, however it is unclear whether ovarian dysfunction precedes anxiety or stress precedes ovarian damage (5). Stress is commonly overlooked as a cause of reproductive vulnerability (2). Activation of the stress response system suppresses the hypothalamic-pituitary-ovarian (HPO) axis (24,25). Daily perceived stress can lead to a decrease in estrogen, progesterone and luteinizing hormone (LH), as well as an increase in follicle-stimulating hormone (FSH) in reproductive-aged patients (24). Patients with a history of depression also had higher FSH and LH levels and lower estradiol levels and those having more significant depressive symptoms were twice as likely to experience earlier perimenopause transition than those without such history (25). Additionally, female patients may be more sensitive to lower levels of cortisol than male patients due to increased limbic system activation following repeated stressors (26). The psychological distress caused by decreased ovarian function may further exacerbate the association between psychological stress and impaired ovarian function (Fig. 1; Table I).

Decreased assisted reproductive technology (ART) outcome. In assisted reproductive medicine, one of the most controversial areas is the underlying influence of psychological factors on pregnancy outcomes. Infertility is a serious health problem around the world and female infertility factors account for at least 35% of all infertility cases (27). The risk of anxiety, depression and distress is generally high in infertile patients (28,29). A 2004 study that interviewed 122 patients before their first infertility clinic visit utilizing a structured psychiatric interview found that 40.2% had a psychiatric disorder, including major depressive, generalized anxiety and dysthymic disorder (30). Volgsten *et al* (31) reported that, of 413 infertile patients undergoing IVF treatment, 127 (30.8%)

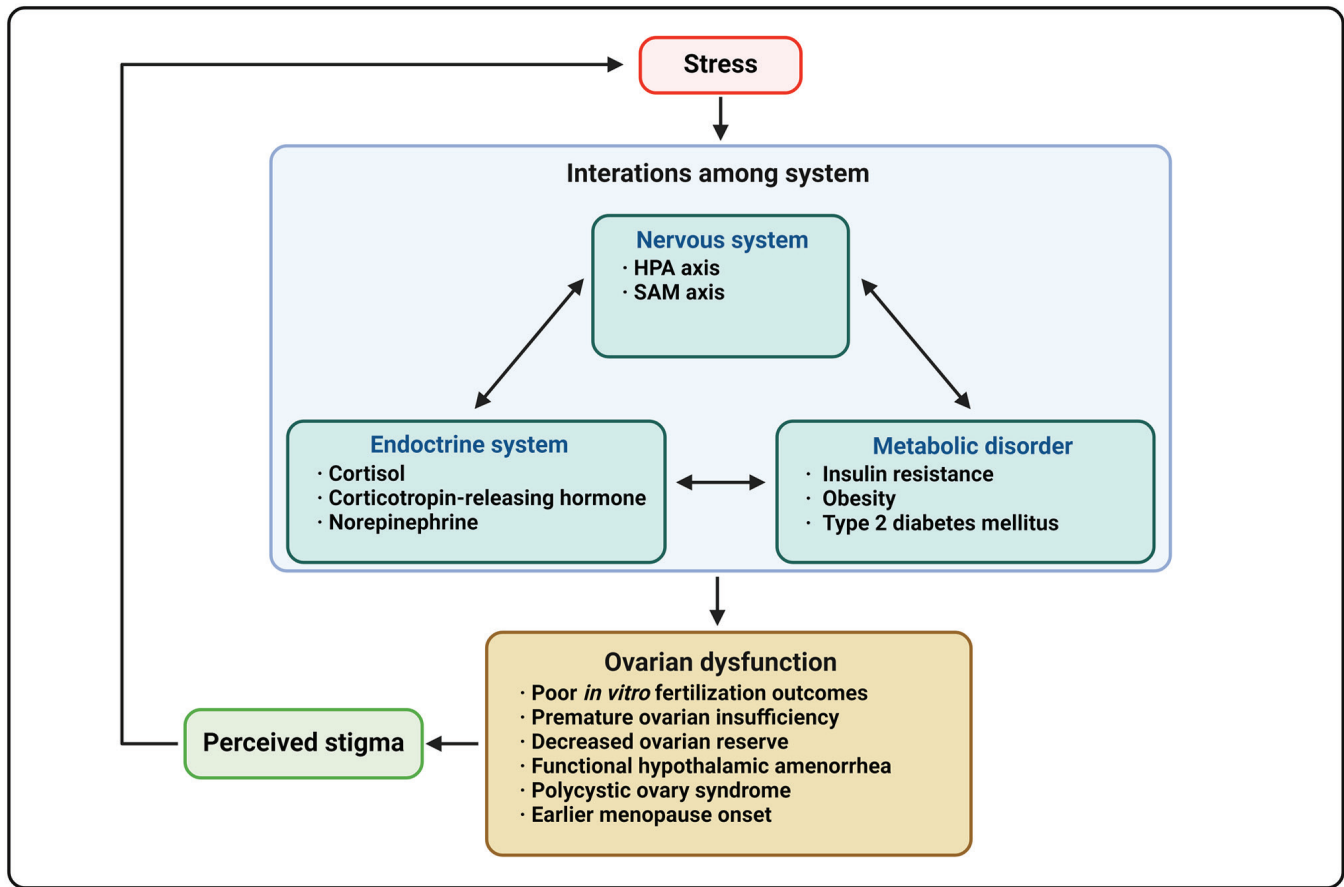


Figure 1. Association between elevated psychological stress and diminished ovarian function. Mental stress triggers the interaction between the nervous and the endocrine system, leading to metabolic disorder. These elements interact with each other, creating a NEM network that results in impaired ovarian function; feelings of shame caused by ovarian insufficiency further exacerbate the psychological burden, ultimately establishing a harmful loop of psychological stress and ovarian dysfunction. Figure generated by using BioRender.com. NEM, neuroendocrine-metabolic; HPA, hypothalamic-pituitary-adrenal; SAM, sympathetic-adrenal-medullary.

were diagnosed with psychiatric disorders, with major depression being the most common. In a study involving 352 female and 274 male patients attending infertility clinics in northern California, 56.5% of patients exhibited notable symptoms of depression and 76% showed notable symptoms of anxiety (32). Infertile patients have higher Beck Depression Inventory (BDI) (14.94 ± 12.90 vs. 8.95 ± 10.49 , $P < 0.0001$) and Spielberger Trait Anxiety Inventory (STAI-T) score (48.76 ± 10.96 vs. 41.18 ± 11.26 , $P < 0.0001$), indicating a greater experience of anxiety and depression compared with fertile individuals (33).

Numerous studies have explored the link between psychological symptoms before and during ART cycles and subsequent pregnancy rates, yielding conflicting results: Certain studies suggest that higher distress/anxiety/depression levels before and during treatment are associated with lower pregnancy rates (8,9,11,34-39), while others do not (10,40-50). These inconsistencies may be attributed to challenges in accurately assessing stress levels in female patients with infertility and heterogeneity of studies (5,28). Future research should therefore focus on developing more precise psychological assessment methods and establishing consistent time points for data collection to enhance quality of research findings.

POI. POI is characterized by premature loss of ovarian function and permanent cessation of menstruation before the age

of 40 years (51). Demographic studies confirm that psychological stress, such as emotional trauma, major life events or chronic stress, may be as a potential trigger for POI in certain cases (52,53). Individuals with POI report continuous exposure to family and work stress and sleep problems, suggesting that adverse life events may contribute to development of POI (52).

Among mental disorders associated with POI, depression is most closely associated to POI. A population study involving 290 patients found that 43% of those with POI had a history of depression, with 26% receiving a depression diagnosis before being diagnosed with POI (15). Depression typically emerges following signs of altered ovarian function but before POI diagnosis (54), possibly due to a more fragile stress system. Female patients are more likely than male patients to develop depression and changes in estrogen levels can increase susceptibility to this condition (18,55). Given the lack of prospective studies on pre-diagnosis stress in patients with POI, more conclusive evidence is needed to determine whether there is an overlapping process or causal association between POI and psychological stress.

Diminished ovarian reserve (DOR). Various indicators are used to assess ovarian reserve (OR), with AFC and AMH being particularly promising (51). A study on 979 premenopausal patients aged 25-45 years used AFC measured via transvaginal

Table I. Impact of psychological stress on ovarian function in population studies.

A, Assisted reproductive technology				
First author (year)	Subjects	Results	Limitations	(Refs.)
Chai <i>et al.</i> , 2023	110 infertile patients; 112 controls	No association between serum cortisol levels and IVF cycles ($\tau=0.071$, $P\geq 0.05$) and clinical pregnancy ($\tau=-0.047$, $P\geq 0.05$).	Cortisol may be influenced by other factors	(42)
Mirzaasgari <i>et al.</i> , 2022	154 infertile patients	No difference in ISE scale between non-pregnant patients and those with positive pregnancy tests	Large drop-off in subjects; low sample size	(44)
Bapayeva <i>et al.</i> , 2021	142 infertile patients	Higher STAI-S and STAI-T are negatively associated with clinical pregnancy (RR=0.95, 95%CI, 0.91, 0.99, $P<0.05$; RR=0.92, 95%CI, 0.86, 0.99, $P<0.05$)	Low response rate; non-response bias	(8)
Peng <i>et al.</i> , 2021	150 patients without clinical pregnancy after first IVF or ICSI; 300 controls	No difference between psychological distress and clinical pregnancy (anxiety, adjusted OR=1.00, 95%CI, 0.97, 1.03; depression, adjusted OR=0.98 95%CI, 0.95, 1.02; perceived stress, adjusted OR=0.98 95%CI, 0.95, 1.01)	Single time point of psychological assessment; small sample size	(45)
Sallem <i>et al.</i> , 2021	79 patients undergoing IVF	BAI score is negatively correlated with embryo segmentation ($r=-0.24$; $P=0.05$) and implantation rate ($r=0.65$; $P=0.001$). No correlation between serum cortisol levels and IVF outcome	No elimination of some confounding factors	(10)
Aimagambetova <i>et al.</i> , 2020	304 infertile patients	Higher STAI-S and STAI-T are negatively associated with clinical pregnancy outcome (OR=0.94, 95%CI, 0.91, 0.98, $P<0.01$; OR=0.95, 95%CI, 0.91, 0.99, $P=0.02$).	Non-response bias; small sample size	(36)
Park <i>et al.</i> , 2019	143 infertile patients	No difference in clinical pregnancy between high or moderate and low stress (FOR=1.11, 95%CI, 0.58, 2.14; FOR=1.37, 95%CI, 0.71, 2.67)	Data of baseline chronic stress, life stressors or stress biomarkers was absent	(46)
Cesta <i>et al.</i> , 2018	485 infertile patients	No difference in clinical pregnancy between lowest and highest categories of perceived stress score (OR=1.04, 95%CI, 0.58, 1.87)	Single time point of psychological assessment; other factors may influence cortisol	(43)
Xu <i>et al.</i> , 2017	842 patients undergoing IVF	Fertilization rate decreases with higher SAS score (91.9%, SAS score, 25-44 vs. 90.4%, SAS score, 45-59 vs. 81.8%, SAS score 60-100], $P<0.001$)	Non-response bias; single time point of psychological assessment	(9)
Terzioglu <i>et al.</i> , 2016	217 couples undergoing ICSI	Patients with positive pregnancy outcome had lower depression score ($P<0.05$)	Small sample size	(35)
Lynch <i>et al.</i> , 2014	501 couples	Patients with high SAA levels have a longer time to pregnancy (FOR=0.71, 95%CI, 0.51, 1.00, $P<0.05$) and double the infertility risk (RR=2.07, 95%CI, 1.04, 4.11)	Single time point of psychological assessment; saliva sample collection	(181)

Table I. Continued.

A, Assisted reproductive technology				
First author (year)	Subjects	Results	Limitations	(Refs.)
Butts <i>et al</i> , 2014	52 patients undergoing IVF	No association between urine cortisol and clinical pregnancy ($\beta=-0.18$, 95%CI, -0.04, 0.02, $P=0.48$).	Small sample size; single time point of uterine sample collection	(50)
An <i>et al</i> , 2013	264 patients undergoing IVF or ICSI	STAI score is negatively associated with live birth rate (OR=0.855, 95%CI, 0.810, 1.006, $P=0.03$).	Response bias; small sample size	(34)
Turner <i>et al</i> , 2013	44 patients undergoing IVF	Patients with positive pregnancy outcome had lower STAI-S score (34.93 vs. 44.35, $P=0.05$), STAI-T 33.67 vs. 41.30, ($P=0.03$) and PSS score (11.53 vs. 16.20, $P=0.03$).	Response bias; small sample size	(37)
Quant <i>et al</i> , 2013	89 patients undergoing IVF and 77 partners	Partner composite psychological distress score was a predictor of fertilization rate ($\beta=-0.18$, SE=0.09, $P=0.049$).	Single time point of psychological assessment	(38)
Pasch <i>et al</i> , 2012	202 patients undergoing IVF	STAI (39.96 vs. 41.41, $P=0.43$) and CES-D score (11.29 vs. 12.39, $P=0.48$) show no difference between patients with successful and unsuccessful outcomes	Data of psychotherapy treatments was absent; follow-up period was short	(41)
Lynch <i>et al</i> , 2012	339 patients trying to conceive	No association between baseline psychosocial and pregnancy rate	Response bias; short follow-up period	(47)
Li <i>et al</i> , 2011	107 infertile patients	Follicular noradrenaline levels are negatively correlated with embryo quality ($r=-0.62$, $P<0.05$) and not correlated with pregnancy rate	Small sample size; insufficient sample representativeness	(180)
Anderheim <i>et al</i> , 2005	166 patients undergoing IVF	No difference in psychological effects between patients with or without adverse pregnancy outcomes	Response bias	(48)
Klonoff-Cohen <i>et al</i> , 2001	151 patients with primary or secondary infertility	Each PANAS unit increase is linked to 2% fewer oocytes retrieved (log-coefficient, -0.019, 95%CI, -0.03, -0.01, $P=0.04$).	Small sample size	(11)
Csemiczky <i>et al</i> , 2000	22 infertile patients	Patients with negative IVF outcome had higher state anxiety level ($P<0.06$).	Small sample size	(39)
Milad <i>et al</i> , 1998	40 patients undergoing IVF	No difference in STAI score (42.15 vs. 45.0) and cortisol levels (2.69 vs. 3.12) between patients with or without adverse pregnancy outcomes	High dropout rate	(49)
B, POI				
First author (year)	Subjects	Results	Limitations	(Refs.)
Sun <i>et al</i> , 2022	43 patients newly diagnosed with POI	Patients with POI consistently experienced adverse life events associated with work, family stress and sleep issues	Small sample size; lack of psychological assessment	(52)
Allshouse <i>et al</i> , 2015	160 patients previously diagnosed with POI	Among patients with POI reporting a history of depression, 26% reported that depression occurred >5 years before POI diagnosis and menopausal symptoms do not diminish over time in patients with POI	Certain confounding factors such as treatment of gonadotoxic drugs, treatment of antidepressants, financial status, smoking and alcohol abuse were not eliminated	(15)

Table I. Continued.

B, POI				
First author (year)	Subjects	Results	Limitations	(Refs.)
Schmidt <i>et al.</i> , 2011	174 patients with spontaneous 46, XX POI; 100 patients with Turner syndrome	Patients with POI have higher lifetime depression rates than patients with Turner syndrome and community-based samples from female subjects ($P<0.001$)	Confounding factors such as such as treatment of gonadotoxic drugs, financial status, postgraduate alcohol abuse; recall bias	(54)
C, Diminished ovarian reserve				
First author (year)	Subjects	Results	Limitations	(Refs.)
Mínguez-Alarcón <i>et al.</i> , 2023	520 patients seeking fertility care	Patients in the second (13.3, 95%CI, 12.7, 13.8) and third (13.5, 95%CI, 13.0, 14.1) tertiles of stress have lower AFC compared with patients in the lowest tertile (14.3, 95%CI, 13.8, 14.9, both $P<0.05$)	Response bias; single time point of psychological assessment	(13)
Golenbock <i>et al.</i> , 2020	332 patients with history of MDD; 644 controls	Depression is negatively associated with AMH levels in patients aged 36-40 years (adjusted PR=0.75, 95%CI, 0.52, 1.09) and nulliparous patients (adjusted PR=0.77, 95%CI, 0.59, 1.00)	Cross-sectional design; unrepresentative population sample	(14)
Dong <i>et al.</i> , 2017	576 infertile patients	SAA is negatively associated with AMH levels ($r=-0.336$, $P<0.0001$; adjusted for age, $r=-0.336$, $P<0.0001$)	Only one biomarker for stress assessment	(58)
Bleil <i>et al.</i> , 2012	979 patients aged 25-45 years	Higher stress levels are associated with higher AFC ($\beta=0.545$, $P=0.005$) and accelerated follicle loss	Single time point of AFC assessment	(56)
Bleil <i>et al.</i> , 2012	683 patients aged 25-45 years	Psychological stress accelerates AFC decline in patients with low ($\beta=-0.070$, $P=0.021$) but not high positive affect ($\beta=0.018$, $P=0.54$)	Response bias; unrepresentative population sample	(57)
D, FHA				
First author (year)	Subjects	Results	Limitations	(Refs.)
Dundon <i>et al.</i> , 2010	41 patients with FHA; 39 healthy controls	Patients with FHA have higher depression and anxiety scores in Zung Scale (both $P<0.001$)	Cross-sectional design; response bias	(63)
Lawson <i>et al.</i> , 2009	13 patients with FHA; 18 amenorrheic patients with anorexia nervosa; 21 healthy controls	Patients with FHA have higher cortisol levels (9.4 vs. 7.6, $P=0.04$) and HAMD (6.6 vs. 1.1, $P<0.001$) and HAMA score (7.5 vs. 1.5, $P<0.001$) compared with healthy controls	Cross-sectional design; response bias	(16)
Bomba <i>et al.</i> , 2007	20 patients with FHA; 20 healthy controls	Both normogonadotropic and hypogonadotropic patients with FHA have higher cortisol levels (16.0 vs. 10.1 and 15.8 vs. 10.1, respectively; both $P<0.01$)	Small sample size	(61)

Table I. Continued.

D, FHA				
First author (year)	Subjects	Results	Limitations	(Refs.)
Marcus <i>et al</i> , 2001	28 patients with FHA; 24 patients with organic amenorrhea; 25 healthy controls	Patients with FHA have higher BDI (7.9 vs. 2.9, $P=0.02$) and HAMD score (6.2 vs. 2.4, $P=0.02$)	Response bias	(62)
Berga <i>et al</i> , 1997	19 patients with FHA; 19 patients with other anovulation causes; 19 healthy controls	Patients with FHA have higher cortisol levels than those with other anovulation causes (80.1 vs. 67.7, $P<0.05$) or healthy controls (80.1 vs. 67.1, $P<0.05$).	Cortisol may be influenced by other factors	(168)

IVF, *in vitro* fertilization; ISE, Infertility Self-Efficacy; STAI, State-trait Anxiety Inventory; RR, relative risk; PR, prevalence ratio; CI, confidence interval; ICSI, intracytoplasmic sperm injection; OR, odds ratio; SAS, Self-Rating Anxiety Scale; SAA, salivary α amylase; PSS, Perceived Stress Scale; CES-D, Center for Epidemiologic Studies Depression; PANAS, Positive and Negative Affective Scale; POI, premature ovarian insufficiency; AMH, anti-Müllerian hormone; AFC, antral follicle count; MDD, major depressive disorder; FHA, functional hypothalamic amenorrhea; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

ultrasound to evaluate OR; the finding indicated a positive association between higher stress levels and AFC in younger patients ($\beta=0.545$, $P=0.005$), and stress accelerates age-related AFC decline ($\beta=-0.036$, $P=0.031$), suggesting women with higher stress experienced faster AFC loss (56). Environmental stress might enhance fertility temporarily by increasing the volume of growing follicles, potentially depleting OR in the long-term (56). Additionally, a cross-sectional study suggested that psychological stress accelerates AFC decline ($\beta=-0.070$, $P=0.021$), implying that low positive affectivity may aggravate the adverse impact of stress on AFC decline (57). Consistent findings across populations reveal that higher levels of perceived stress are linked to decreased AFC and AMH levels (13). A cross-sectional study on 576 infertile patients demonstrated a negative association between salivary α amylase (SAA), a stress marker, and AMH levels ($r=-0.315$, $P<0.001$; adjusted for age, $r=-0.336$, $P<0.001$) (58). Another study noted modest inverse associations between depression and low AMH among patients aged 36-40 years (adjusted $P=0.75$, 95%CI, 0.52, 1.09) and nulliparous patients (adjusted $P=0.77$, 95%CI, 0.59, 1.00) (14). Taken together, data from the aforementioned population studies suggested that elevated levels of perceived stress, as well as biomarkers of stress, are associated with reduced OR.

FHA. FHA or anovulation is characterized by the absence of menstruation and ovulation without an identifiable organic cause. The main determinant of the disease is a combination of psychosocial and metabolic stress (59). Predisposing factors include low energy use, nutritional deficiencies, abnormal sleep, emotional and chronic severe stress and overexertion or physical activity (59,60). More severe depressive and anxious symptoms contribute to onset of FHA (16,61-63). Patients with FHA often exhibit dysfunctional attitudes, such as perfectionism, higher need for approval, and struggle to

cope with daily stressors (59). Cognitive behavioral therapy accelerates the recovery of ovarian function in patients with FHA, underscoring the role of mental stress in development of this condition (59). As with POI, more prospective studies are needed to explore the effect of psychological stress on FHA.

PCOS. PCOS is a prevalent endocrine disorder in patients of reproductive age, characterized by systemic metabolic issue and disruptions in neuroendocrine-immune function (64). Patients with PCOS are at a higher risk of developing cardiovascular risk factors and associated insulin resistance, dyslipidemia and diabetes (65). Patients with PCOS also face an elevated likelihood of mood and anxiety disorders (17,66,67). There is a notable prevalence of psychiatric issues among patients with PCOS, including depression (26-40%), anxiety (11.6%) and binge-eating (23.3%) (17), indicating a potential role of psychological factors in pathophysiology of PCOS. Psychological aspects have been identified as a notable risk factor for PCOS (68) and emotional distress potentially stems from psychosocial and/or pathophysiological origins (66). Moreover, patients with PCOS may perceive symptom such as hirsutism and acne or potential outcomes such as infertility and obesity as stigmatizing, leading to distress and potentially exacerbating progression of the disease (67). However, as meta-analysis has indicated, few studies have focused on the effect of psychological stress on disease and PCOS (17).

4. Stress models and ovarian dysfunction

Animal models (69-71), in which the effects of mental stress can be observed, are widely used for studying pathogenesis of stress-related disorders, such as type 2 diabetes, systemic inflammation, obesity and cancer, and their treatment strategies (Fig. 2; Table II).

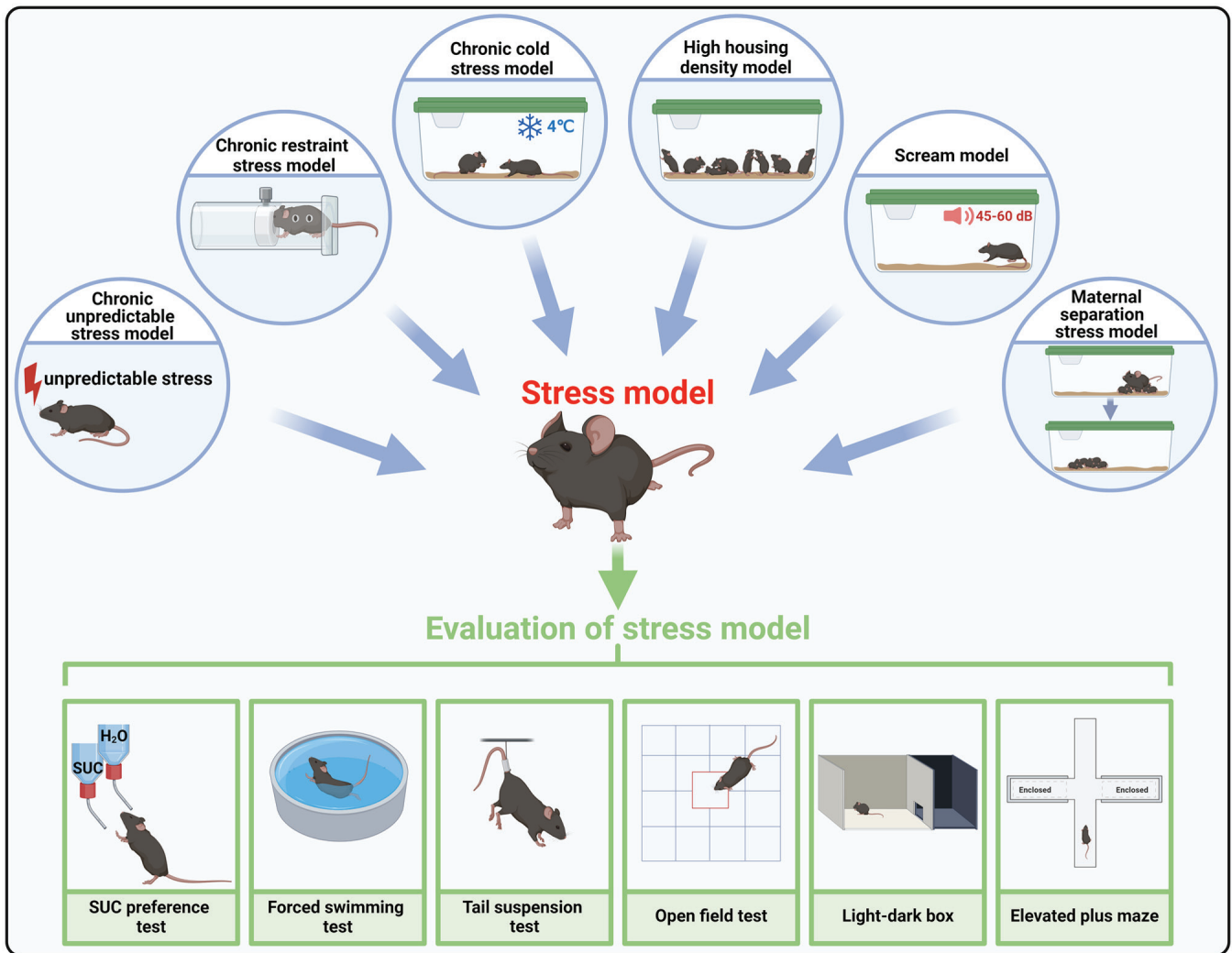


Figure 2. Models used in stress-associated ovarian function studies and stress assessment methods. Chronic unpredictable stress and chronic restraint stress models are the most widely used. The cold stress model is primarily applied to examine sympathetic-adrenal-medullary activation effects on the ovary. Additional models, such as high housing density, scream and maternal separation models, are also used to analyze impact of stress on ovarian function. The appropriate modeling method is selected based on experimental requirements and conditions. Following stress modeling, animals displaying anxiety and depression characteristics are assessed using methods such as SUC preference, forced swimming, tail suspension, open field, light-dark box and elevated plus maze tests. The figure was created with BioRender.com. SUC, sucrose.

Stress models of ovary research

CUS. CUS is a well-established method where animals are subjected to unpredictable stressors over a prolonged period to induce emotional changes, which lead to lasting alterations in animal behavior, gut microbiota and neurological function (72-74). The CUS stressors include restraint stress, tail suspension and swimming, with the intensity of stressors gradually increasing to prevent tolerance (19). Depression-like behaviors induced by CUS are evaluated using tests such as the forced swimming test (FST) and sucrose preference test (SPT) (75). CUS exposure has been shown to disrupt the estrous cycle, decrease the number of primordial and preantral follicles and corpus luteum, elevate serum FSH and cortisol levels and reduce serum estradiol, AMH and gonadotropin-releasing hormone (GnRH) levels, making it an ideal animal model for studying impaired ovarian function (19,76-80).

CUS has been found to negatively impact oocyte developmental potential, with transcriptome analysis revealing disruption in expression of apoptotic genes and cell cycle

regulators (81). CUS decreases brain-derived neurotrophic factor (BDNF) expression in antral follicles, resulting in decreased number of retrieved oocytes and rate of blastocyst formation, which could be rescued by exogenous BDNF treatment (82). Another study indicated that CUS significantly decreased the number of retrieved oocytes, fertilization rate and number of embryos (including high-quality embryos and blastocysts), which may be due to different expression of heat shock protein 70 in the embryo after CUS (83). Additionally, supplementation with exogenous growth differentiation factor 9 (GDF9) rescues development of both secondary and antral follicles in stressed mice (84). Granulosa cells in the ovary of depression-like mice induced by CUS exhibit increased apoptosis, possibly due to accumulation of reactive oxygen species (ROS) and activation of the mitogen-activated protein kinase (MAPK) pathway resulting from downregulation of isocitrate dehydrogenase-1 expression (85,86). This suggests CUS can lead to elevated ovarian oxidative stress and mitochondrial

Table II. Summary of animal models for ovarian dysfunction induced by psychological stress.

Animal	Stress	Behavior test	Stress biomarker	Effects on ovary	(Refs.)
C57BL/6 or BALB/c mice	8 week CUS	N/A	Increased serum corticosterone levels	Decreased follicle number; irregular estrous cycle; increased serum FSH levels; decreased estradiol, progesterone and AMH levels	(19,85)
C57BL/6 mice	2-8 month CUS	SPT, TST	Increased serum corticosterone levels	Decreased follicle number; increased follicular atresia and ovarian fibrosis; irregular estrous cycle; decreased estradiol and AMH levels and litter size	(77)
Kunming mice	3-4 week CUS	OFT	Increased serum corticosterone and CRH levels	Decreased number of retrieved oocytes and oocyte quality; increased follicular atresia	(83,88)
ICR mice	6 week CUS	SPT, OFT	Decreased serum corticosterone and CRH levels	Decreased oocyte fertilization, cleavage and blastocyst formation rate	(81)
Swiss mice	5 or 30 day CUS	OFT, SPT, FST, EPM	Increased serum corticosterone levels	Inhibition of follicular development; increased follicular atresia rate; irregular estrous cycle	(82,84, 87)
Sprague-Dawley rats	4-5 week CUS	SPT, OFT	N/A	Irregular estrous cycle; increased ovarian fibrosis, follicular atresia and FSH levels; decreased estradiol and AMH levels	(76,79, 80)
C57BL/6, BALB/C or Kunming mice	4-8 week CRS	N/A	Increased serum corticosterone and CRH levels	Decreased oocyte quality; increased follicular atresia rate; irregular estrous cycle	(20,21, 93,98, 104)
Sprague-Dawley rats	5 day CRS	N/A	N/A	Decreased progesterone levels; increased fetal resorption	(99)
Kunming mice	24 or 48 h CRS	N/A	Increased serum corticosterone and CRH levels	Decreased oocyte quality; impaired spindle assembly	(97,100, 101,103, 105)
Sprague-Dawley or Wistar rats	4-12 weeks cold stress	N/A	Increased ovarian NE concentration and serum corticosterone levels	Decreased number of follicles, ovulation and oocyte maturation rate; irregular estrous cycle	(106,107, 111,112, 114, 118)
Sprague-Dawley or CIIZ-V rats	3-8 week cold stress	N/A	N/A	Unchanged estrous cycle and ovarian tissue structure	(117, 119)
C57BL/6 mice	10 week cold stress	N/A	Increased serum corticosterone levels	Increased number of atretic follicles; decreased serum AMH levels	(120)
Sprague-Dawley rats	3 week scream sound exposure	SPT, FST	Increased serum corticosterone levels	Decreased AMH and estradiol levels and litter size; increased follicles loss and granulosa cell apoptosis	(121)
NMRI mice	14 day maternal separation stress	N/A	N/A	Impaired follicle development; decreased oocyte maturation rate	(122)
Kunming mice	24 h predatory stress	EPM	Increased serum corticosterone levels	Decreased oocyte quality and embryo development	(126)

CUS, chronic unpredictable stress; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone; SPT, sucrose preference test; OFT, open field test; TST, tail suspension test; CRH, corticotropin-releasing hormone; FST, forced swimming test; CRS, chronic restraint stress; NE, norepinephrine; EPM, elevated plus maze.

dyshomeostasis, supported by increased expression of superoxide dismutase (SOD), mitochondrial fusion protein optic atrophy 1, mitofusin 1 and nucleus-encoded protein

succinate dehydrogenase complex A and decreased expression of mitochondrial fission protein 1 in ovary of stressed mice (87,88).

CRS. The CRS model, which is commonly used in studies (89-91) on psychological stress, involves confining animals in a restraint bucket for a designated period each day, inducing anxiety and depression. Typically, animals are restrained for 4 h daily over an 8-week period (20), although the number of restraint days and duration/day can be tailored based on experimental objectives and specific circumstances (92). For example, for studying social interaction, a restraint duration of 5 min is sufficient, however, if the aim is to observe changes in the brain, the restraint time needs to be extended to 6 h (92).

Mice subjected to CRS display elevated serum cortisol and corticotropin-releasing hormone (CRH) levels, indicating activation of the hypothalamic-pituitary-adrenal (HPA) axis (21,93-98). Additionally, CRS results in decreased ovarian weight, disruption in estrous cycles, increased ovarian fibrosis and overactivation of primordial follicles, which may be attributed to the upregulation of Kit expression and activation of the phosphatidylinositol 3-kinase (PI3K)/PTEN/Akt pathway (21). CRS increases oocyte aneuploidy, decreases the percentage of blastocysts and number of cells/blastocyst and impaired corpora lutea function during gestation in mice and rats, leading to decreased pregnancy rates and litter size (99-101). The decline in fertility associated with CRS may be linked to diminished oocyte quality, with germinal vesicle breakdown (GVBD) being a key indicator of oocyte quality (102). Following CRS, female mice exhibit compromised oocyte competence, which was characterized by an increase in spindles defects and chromatin misalignment, decrease in GVBD percentage and prolonged GVBD time, which may be due to abnormalities of the Fas/FasL system or TNF- α signaling in oocytes and granulosa cells (93,97,98,103,104). Moreover, CRS decreases the expression of cyclin B1 (CCNB1), a key regulator of M-phase/mature promoting factor (93). Treatment with MG132, an inhibitor of anaphase-promoting complex/cyclosome, rescues prolonged GVBD time and elevates CCNB1 expression in oocytes of CRS-exposed mice (93). Furthermore, CRS elevates meiotic arrest failure in oocytes by suppressing the cyclic AMP (cAMP) signaling pathway, particularly via the downregulation of G-protein-coupled receptor 3, natriuretic peptide C and natriuretic peptide receptor 2, leading to accelerated oocyte loss and premature ovarian aging (20). Short-time restraint stress accelerates postovulatory oocyte aging due to elevated cytoplasmic calcium levels and increased oxidative stress (105).

Chronic cold stress. Animals exposed to cold stress experience heightened sympathetic activity and elevated levels of norepinephrine in the ovary (106-108), while corticosterone and gonadotropin (Gn) levels are unaffected (109,110). As a result, chronic cold stress is commonly used in the examination of overactivation effects of the sympathetic-adrenal-medullary (SAM) axis. The cold stress regimen typically spans 21-28 days, involving activities such as daily 15-min swims in 15°C water or 3-h exposures to 4°C temperature (111,112).

The majority of studies show that prolonged exposure to cold stress may result in extended estrous cycle, reduced level of estrogen and progesterone, decreased corpus luteum count and increased follicular atresia in rats (111,113-115). The observed hindered follicular development may be attributed to increased nerve growth factor levels in the ovary stemming

from sympathetic activation, breakdown of the gap junctions between oocyte and cumulus cells and dysregulation of the NRF2/Connexin-43 (CX43)/steroidogenic acute regulatory (StAR)/progesterone pathway in granulosa cells following cold exposure (106). Cold stress triggers the upregulation of endothelin-1 (ET-1) and ET-receptor type A, alongside down-regulation of ET-receptor type B protein, thereby disrupting the ovarian vascular endothelin system, leading to vasoconstriction and microcirculation issues in rats (113). This compromised blood flow may impede ovarian function by decreasing oxygen and nutrient delivery to the ovary (116). However, a previous study indicated that prepubertal rats that experience chronic cold stress do not exhibit altered ovarian architecture that affects the ovulation in adulthood (117). When animals were exposed to both chronic restraint and cold water stress, the results were different (118,119): A study showed that the number of atretic follicles and the percentage of apoptotic granulosa cells are notably increased following exposure to restraint stress, while another study indicated that there were no effects on the ovaries after exposure to cold stress (118,119).

Other stress models. A model of high housing density is conducted by housing eight C57BL/6 mice in a 484 cm² ventilated cage which results in increased stocking density and elevated stress hormones among the mice (120). Mice housed in more densely packed conditions exhibit higher corticosterone and lower AMH levels, alongside a great number of atretic ovarian follicles (120). The scream model subjects mice to noise levels between 45 and 60 dB for 6 h daily over 3 weeks, leading to decreased levels of AMH and estradiol, loss of primordial and preantral follicles, increased apoptosis in granulosa cell and ultimately decreased litter sizes (121). An additional study indicated that maternal separation stress could simulate early life stress (122), with population studies suggesting that early life stress may be associated with an earlier onset of menarche and menopause (123-125). In a previous study, female litters were separated from their mothers between postnatal days 2 and 16 for 6 h/day, with the home cages of the litters placed on a warming pad set at 33-35°C to prevent undue stress (122). After 14 days, there was a significant decrease in the activity of SOD, glutathione peroxidase and catalase, accompanied by oocyte development disorder (122). A predatory stress model suggests that the rate of blastocyst of formation, and the number of cells/blastocyst significantly decreases in stressed mice (126). Chronic immobilization stress could disrupt the estrous cycle, decrease serum levels of AMH, increase the serum levels of FSH and cortisol and reduce the number of primordial follicles (127). In addition, cortisol injection simulates the impact of stress-induced cortisol elevation on ovarian function (128).

While animal models enhance the current understanding of psychiatric disorders, they have certain limitations; for example, animals are incapable of conveying sadness, guilt or suicidal thoughts, which are symptoms mostly confined to humans (129).

Evaluation of stress models. Following successful modeling, the experimental animals display indications such as anhedonia and melancholy, in addition to other signs of depression such as disturbed sleep, alterations in weight and appetite,

anxiousness and isolation from social interaction, mirroring the symptoms observed in humans with major depressive disorder (130).

SPT. SPT is frequently utilized to evaluate anhedonia (131-133). Test subjects are provided with a choice between water sources containing sucrose or plain water; decreased appetite for sucrose is considered to indicate anhedonia (131).

FST. To evaluate behaviors associated with hopelessness, FST is employed. The animal is positioned in a cylinder filled with water; if the subject recognizes that escape is unattainable, it may exhibit depressive-like behavior characterized by limited movement except that necessary to keep the snout above the water level (134).

Tail suspension test (TST). TST is a common method for assessing depressive-like behavior, with the time spent motionless by the subject over a 6-min period recorded (135).

Open field test (OFT). OFT detects the locomotor activity and exploratory behavior (136). Upon introduction to a new open field, animals display fear of the unfamiliar surroundings by staying along the outer edges, although curiosity spurs them to venture further into the center (137,138). In general, mice tend to hug the walls due to thigmotaxis, moving primarily along the perimeter (137). This behavior is amplified in mice exhibiting anxiety-like traits; mice with lower anxiety levels are inclined to spend more time in the central, open region of the field (137).

Light-dark box (LDB). LDB box test exploits instinctual aversion to well-lit areas and spontaneous exploration in response to mild stressors, such as novel environments and light exposure (139). The delay in a mouse entry into the dark section indicates an avoidance of the bright area due to anxiety, while movements between compartments reflect exploratory behavior.

Elevated plus maze (EPM). EPM is extensively utilized for evaluating anxiety-related behavior in laboratory animals, particularly rodents (140-142). Similar to OFT and LDB, EPM exploits the emotional adaptive responses that animals exhibit when confronted with unavoidable aversive situations (143).

Commonly used models for ovarian function research. Recent studies (75,85,98) exploring the effects of mental stress on ovarian function have predominantly employed CUS and CRS models. Animals exposed to stress in these models exhibit decreased preference for sucrose in the SPT and total distance traveled and locomotor activity duration and increased time spent in the peripheral zones during OFT. On the other hand, the cold stress mode primarily activates the SAM system and does not significantly alter mouse behavior and is more appropriate for studying the effects of stress-induced sympathetic nervous activation on ovarian function. These models not only induce depression-like behaviors but also affect ovarian function, such as irregular estrous cycle, decreased ovarian reserve. Thus, they provide a more comprehensive reflection of the impact of psychological stress on ovarian function.

5. Mechanism of ovarian dysfunction caused by mental stress

During the stress response, the autonomic nervous system reacts instantly by triggering the SAM axis and activating the HPA axis (144). Stimulation of autonomic nerves prompts release of norepinephrine (NE) from neuronal terminals, leading to the activation of the adrenal medulla and subsequent discharge of epinephrine, resulting in activation of the SAM axis (145). The activation of the hypothalamic paraventricular nucleus (PVN) in the brain induces release of CRH and arginine vasopressin (AVP) into the pituitary portal system. CRH and AVP synergistically stimulate secretion of pituitary adrenocorticotrophic hormone, which enters the systemic circulation, reaches the adrenal cortex and promotes the production and release of cortisol (146). Additionally, CRH that is released from the PVN area of the inferior colliculus can activate locus coeruleus neurons, increasing NE production (147). The neuroendocrine system serves critical roles in regulating basal homeostasis and responding to threats and it is also involved in the pathogenesis of diseases marked by imbalance or dyshomeostasis (148-150). Prolonged exposure to life stressors in individuals with a susceptible genetic makeup can lead to visceral fat build-up, attributed to persistent hypercortisolism, reactive insulin hypersecretion and reduced growth hormone secretion (68). Furthermore, in adults, stress can induce hypogonadism, and lead to symptoms such as loss of libido and subfertility (68).

Elevated levels of cortisol have the potential to disturb the equilibrium of hormones key for reproductive function, such as GnRH, LH and FSH, leading to a disruption in ovarian function (151,152). Additionally, stress hormones released by the SAM axis impact the HPO axis by influencing the secretion of GnRH and other regulatory hormones responsible for ovarian function (145). Furthermore, premature cessation of ovulation may be related to elevated serum triglycerides and high-density lipoprotein cholesterol levels (153). Patients with POI exhibit irregularities in lipid and glucose metabolism (154). Fig. 3 demonstrates associations between psychological stress, HPA and HPO axes, sympathetic adrenal system and metabolic disorders influencing ovarian function, highlighting the role of HPA and SAM axis activation along with metabolic disorder (Fig. 4; Tables III and IV).

HPA axis. The HPA axis serves a key role in the functioning of the neuroendocrine system, overseeing responses to stress and managing bodily functions such as digestion, immunity, mood, sexual behavior and energy regulation (68). Activation of the HPA axis impacts ovarian function by boosting the levels of cortisol and CRH. Additionally, it can suppress release of gonadotropins, such as FSH and LH, thereby affecting synthesis of steroid hormones, ovulation and menstrual cycle (155). Previous research has indicated that the surge in cortisol and CRH resulting from HPA axis activation, along with the inhibition of the HPO axis, are key factors in impairing ovarian function (156).

In a CRS model, activation of the HPA axis results in impaired oocyte developmental potential and decreased fertility (21,93-95). Previous studies indicated that patients undergoing IVF experienced higher levels of state anxiety

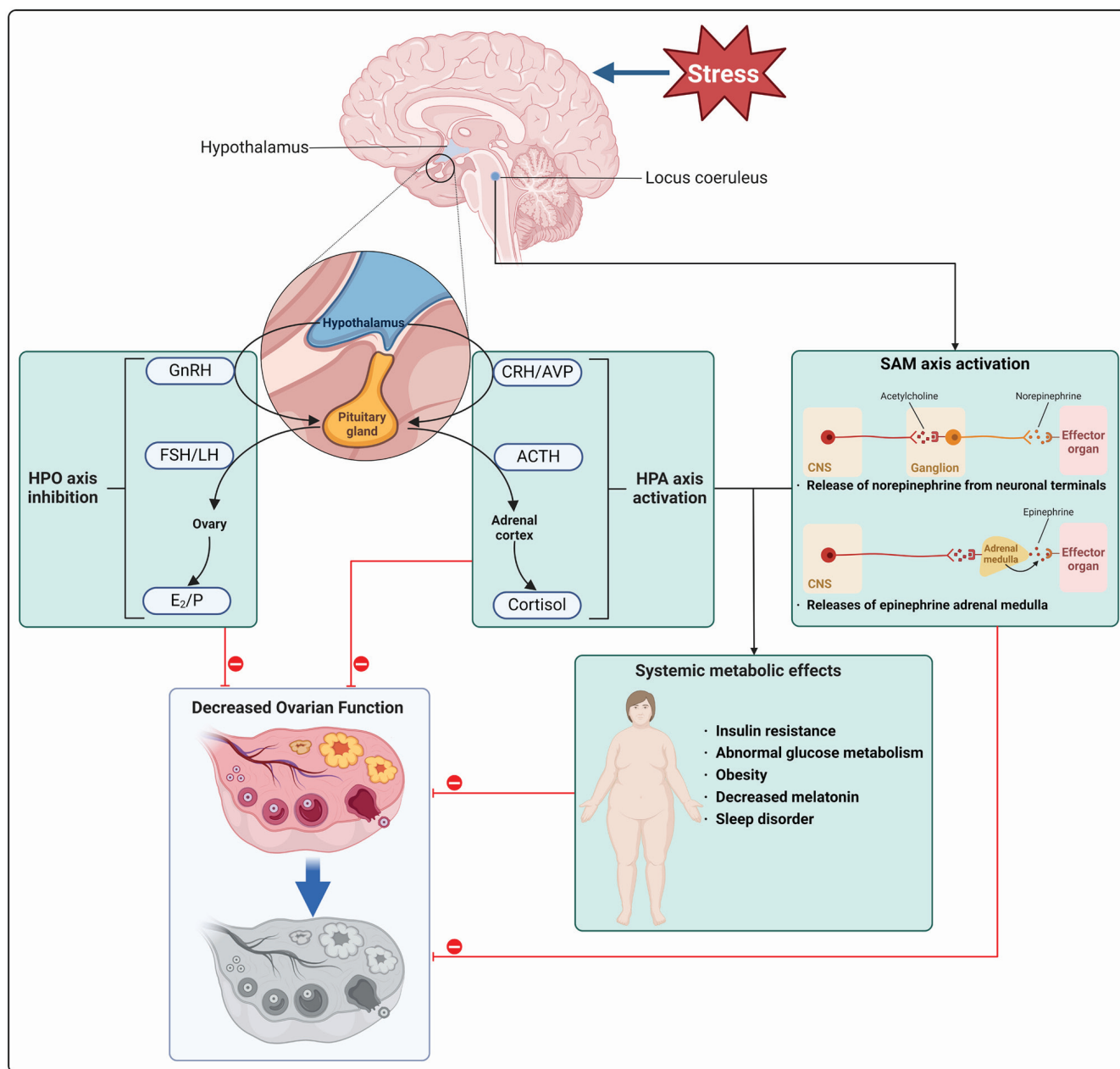


Figure 3. Association between psychological stress, HPA, HPO and SAM axes and metabolic disorder in regulating ovarian function. Psychological stress leads to the activation of the HPA and SAM axes, while concurrently suppressing the HPO axes. In response to stress, activation of the paraventricular nucleus stimulates the secretion of CRH and AVP into the pituitary portal system, stimulating the pituitary gland to release ACTH into the circulation, which triggers cortisol release from the adrenal gland. Simultaneously, the locus coeruleus is activated, resulting in a surge of systemic sympathetic nervous excitement along with increased release of epinephrine from the adrenal medulla. The activation of HPA and SAM axes disrupts neuroendocrine homeostasis, triggering a cascade of metabolic disorders such as glucose metabolism abnormality and obesity. This dysregulation, coupled with the suppression of the HPO axis, impairs ovarian function. Figure created with BioRender.com. HPO, hypothalamic-pituitary-ovarian; HPA, hypothalamic-pituitary-adrenal; SAM, sympathetic-adrenal-medullary; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E₂, estradiol; P, Progesterone; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; CNS, central nervous system.

and serum cortisol (39,157). Additionally, patients with high anticipatory state anxiety and cortisol concentrations have lower pregnancy rates (158), supporting the link between HPA axis activation and decreased fertility. However, a cross-sectional study of 89 infertile patients revealed that increased perceived mental stress is an independent predictor of increasing FSH levels ($\beta=0.22$, $P=0.045$) and likelihood for DOR (OR=9.97, 95%CI, 1.66, 55.99, $P=0.012$), but there was no significant difference in serum cortisol levels between patients with DOR and normal OR ($r=-0.176$, $P=0.287$), which

suggests that serum cortisol levels, representing current stress, may not significantly be associated with ovarian reserve or infertility (159). In direct exposure studies, mouse oocytes exposed to physiological or stress-induced levels of cortisol during *in vitro* maturation did not show any impact on nuclear maturation or embryo development (94,160). Conversely, injection of cortisol into female mice resulted in impaired oocyte development, decreased mitochondrial membrane potential and increased oxidative stress and granulosa cell apoptosis through activating the TNF- α system (128). These effects

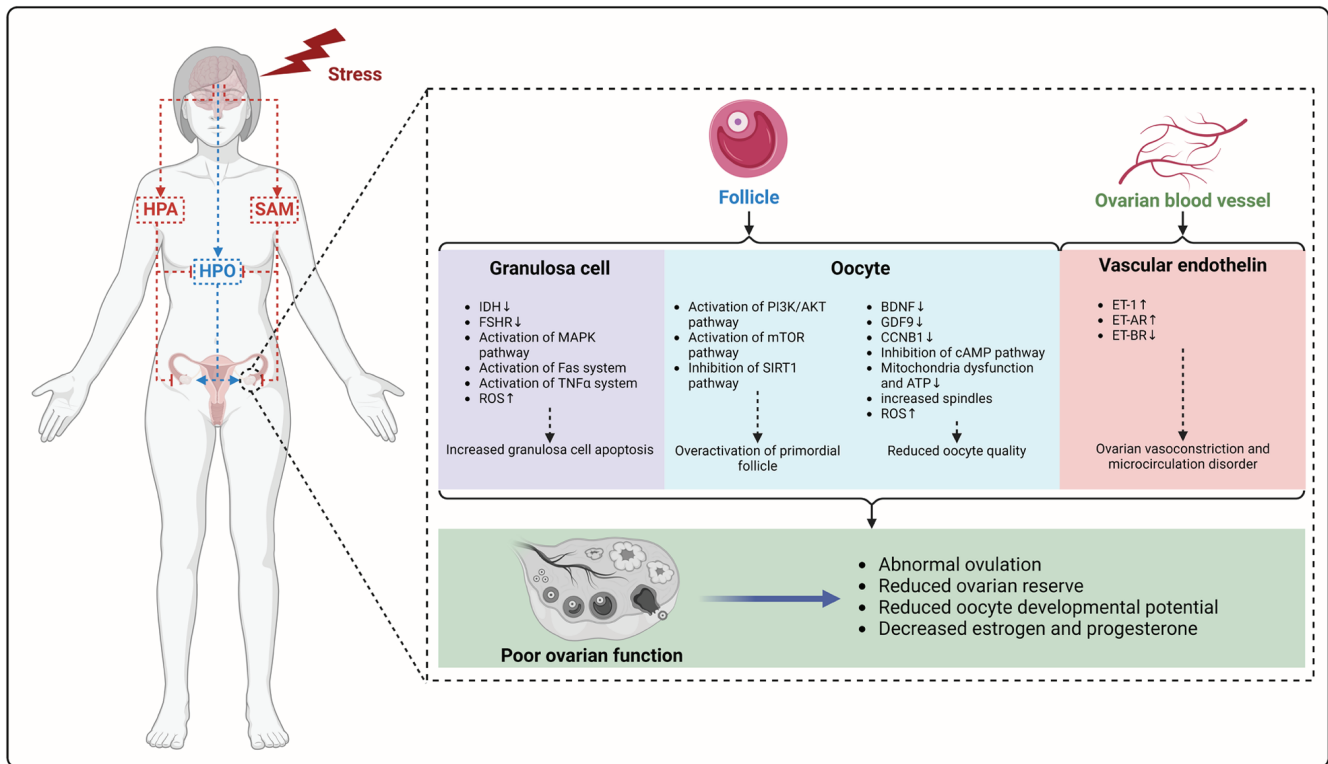


Figure 4. Mechanisms of ovarian dysfunction caused by stress. Psychological stress affects ovarian function and inhibits the HPO axis by activating the HPA and SAM axes. This causes increased granulosa cell apoptosis, diminished oocyte quality and excessive activation of primordial follicles, culminating in decreased ovarian reserve. Meanwhile, psychological stress leads to disorder of the vascular endothelin system of the ovary, resulting in ovarian vasoconstriction and microcirculation disorder. Figure created with BioRender.com. HPA, hypothalamic-pituitary-adrenal; SAM, sympathetic-adrenal-medullary; HPO, hypothalamic-pituitary-ovarian; IDH, isocitrate dehydrogenase; FSHR, follicle-stimulating hormone; ROS, reactive oxygen species; BDNF, brain derived neurotrophic factor; GDF, growth differentiation factor; CCN, cyclin; ET-AR, ET-receptor types A.

may be linked to decreased expression of insulin-like growth factor 1 (IGF-1) and BDNF in granulosa cells and decreased FasL/Fas secretion in ovaries and oocytes (161). The differing impacts of cortisol *in vivo* and *in vitro* may be attributed to the indirect influence of cortisol on oocytes via the NEM network. In rats, exposure to CRS leads to increased expression of hypothalamic RFamide-related peptide-3 (RFRP3) and levels of circulating corticosterone, resulting in decreased HPG axis function (95). However, following a complete estrous cycle, female rats exhibit decreased inclination towards mating; the stress-induced reproductive dysfunction in female rats is alleviated by suppressing RFRP3 expression using a cytomegalovirus promoter-driven lentivirus vector. This indicates that elevated levels of RFRP3 under stress may have enduring detrimental impacts on fertility (95).

During stress, the hypothalamus produces a neuropeptide known as CRH, which serves a vital role in the regulation of ovarian functions, as its receptors have been identified in reproductive organs, including ovary, uterus and placenta (162). Previous research has shown that CRH is responsible for activation of primordial follicles in cultured newborn mouse ovaries *in vitro* (21). Furthermore, CRS could result in a decrease in oocyte competence and an increase in both CRH and CRH receptor (CRH-R) expression in the ovary (97). Co-culturing mouse granulosa cells with CRH activates the Fas/FasL and TNF- α systems, leading to heightened apoptosis of granulosa cells and oocytes, as well as impaired early embryonic development (97,103). CRH-R antagonists such as antalarmin are

effective in inhibiting these damaging effects (97). In another study, injection of CRH in female rats for 12 days post-mating resulted in a 40% disruption in pregnancy (163). These findings suggest that CRH negatively impacts reproductive function.

Stress-induced activation of the HPA axis results in increased levels of glucocorticoids in the bloodstream, along with disrupted functioning of the HPO axis and ovarian cycle. In female mice, chronic stress reduces the synthesis and release of LH mediated by GnRH (164). One explanation for decreased LH secretion may be the elevated levels of cortisol due to stress. A previous study on mice exposed to long-term corticosterone demonstrated a notable decrease in LH levels, accompanied by alteration in neuronal activity in the pituitary gonadotroph cells (165). CRS in rats inhibits the preovulatory LH surge (166), while CUS has been shown to raise cortisol levels and SOD activity (87), both of which impact ovulation. Moreover, patients diagnosed with FHA exhibit high activation of the HPA axis, indicated by increased levels of cortisol in the blood (167). Furthermore, patients with FHA who experience spontaneous recovery of ovarian function show lower serum cortisol levels post-recovery compared with those who do not recover from FHA (168).

SAM axis. Ovarian function is regulated by the autonomic nervous system, which cooperates with the HPO axis (169). Sympathetic fibers from the celiac ganglia extend to ovarian follicles, mainly targeting the theca layer, where NE, the principal neurotransmitter, interacts with β -adrenergic receptors

Table III. Effect of stress on ovary.

Cell type	Type of stress	Test subject	Mediators	Impact	(Refs.)
Oocyte	CUS	Mice	HPA axis	Increased follicle atresia with suppressed GDF9 expression	(84)
	CRS	Mice	HPA axis	Increased abnormal bipolar spindle rates; reduced the expression of CCNB1; increased meiotic arrest failure of oocytes by inhibition of the cAMP pathway; overactivation of primordial follicles due to activation of the PI3K/AKT pathway	(20,21,93)
	N/A	Rats	NE	Decreased ovarian sympathetic activity decreases KISS1 levels and increases FSHR expression and follicle growth	(177)
	Injection of cortisol	Mice	Cortisol	Impaired oocyte development and mitochondrial membrane potential	(128,161)
Granulosa	CUS	Mice	HPA axis	Increased apoptosis due to the ROS accumulation and MAPK pathway activation	(85)
	CRS	Mice	HPA axis	Increased apoptosis via activating the Fas/FasL and TNF α system	(97,103))
	N/A	Humans	NE	Induced generation of ROS in granulosa cells	(178)
	Injection of cortisol	Mice	Cortisol	Decreased expression of IGF1 and BDNF increased apoptosis	(128,161)
	N/A	Rats	NE	Activation of TGF β -SMAD7 pathway and apoptosis	(179)

CUS, chronic unpredictable stress; HPA, hypothalamic-pituitary-adrenal; GDF9, growth differentiation factor 9; CRS, chronic restraint stress; CCNB1, cyclin B1; cAMP, cyclic AMP; KISS, kisspeptin; FSHR, follicle-stimulating hormone receptor; ROS, reactive oxygen species; NE, norepinephrine; IGF1, insulin-like growth factor 1; BDNF, brain-derived neurotrophic factor; TGF β , transforming growth factor β ; ET-AR, endothelin-receptor type A.

situated in the theca and granulosa cells (170-172). Neural and hormonal signals integrate to control steroid production and development of ovarian follicles (173). Notably, during stressful conditions, excessive activation of the SAM axis disrupts this equilibrium, leading to compromised ovarian function (174).

Previous research on rats has shown that normal aging process is associated with elevated NE levels and increased sympathetic activity within the ovary (175), implying that SAM axis activation promotes ovarian aging. Chronic exposure to cold stress activates the sympathetic nervous system, causing prolonged estrous cycle, decreased levels of estrogen and progesterone and corpus luteum count and heightened follicular atresia in rats (114,115,117,176).

Surgical denervation of the ovary and blocking the β -adrenergic receptor using propranolol decrease ovarian sympathetic activity, leading to a decrease in ovarian kisspeptin (KISS1) and an increase in FSH receptor (FSHR) expression. This may enhance follicle growth, suggesting activation of the SAM axis could hinder ovarian function by elevating ovarian KISS1 levels (177). NE is detected in human follicular fluid (178). However, physiological levels of NE are unable to trigger NE receptor activation but can induce the generation of ROS in granulosa cells (178). *In vitro*, rat granulosa cells display increased apoptosis upon co-culture with NE (179). Furthermore, following recovery from cold stress model, rats exhibited sustained elevated levels of ovarian NE, disrupted estrous cycle and reduced fertility, indicating that SAM axis activation may have lasting impacts on ovarian function in rats (111).

Data from population studies also corroborate the harm caused by SAM axis activation on ovarian function (12,58,180,181). A previous population-based study including 274 patients showed significant decreases in the likelihood of conceiving during the fertile window in the first cycle of attempting pregnancy for patients with high SAA levels compared with those with low levels (fecundability odds ratio, FOR=0.85, 95%CI, 0.67, 1.09) (12). Although SAA is a marker for stress and SAM activity, these findings support the idea that stress impacts female fertility through the SAM pathway (12). Similarly, a study on 401 patients found that those in the top tertile for SAA levels had a 29% decrease in fecundity (longer time to pregnancy) compared with those in the bottom tertile (FOR=0.71, 95%CI, 1.04, 4.11), and this decrease in fecundity leads to an increased risk of infertility (Relative Risk, RR=2.07, 95%CI=1.04, 4.11) (181). Aside from its potential impact on fertility rates, SAM axis activation may also influence OR. A study on 576 infertile patients found that higher levels of SAA were linked to lower serum AMH ($r=-0.315$; adjusted $r=-0.336$, both $P<0.0001$) (58). Another population study involving 107 patients revealed that follicular NE levels had a negative association with proportion of good quality embryos ($r=-0.62$, $P<0.05$) but not with clinical pregnancy rates (180).

Metabolic disorder. The activation of stress-associated neuroendocrine systems plays a key role in maintaining body equilibrium, yet excessive stress can disrupt homeostasis (148). Previous studies indicate that life stress poses a risk and has prognostic implications for metabolic conditions such as

Table IV. Effect of metabolic disorder on the ovary.

First author (year)	Subjects	Effect on ovarian function	Limitations	(Refs.)
Qin <i>et al</i> , 2023	265 infertile patients	T2DM decreases clinical pregnancy rate (adjusted OR, 0.458, 95%CI, 0.235, 0.891, P=0.022) and live birth rate (adjusted OR, 0.227, 95%CI, 0.101, 0.513, P<0.001)	Incomplete medical records; lack of detailed population characteristics	(207)
Sekhar <i>et al</i> , 2015	600 patients (300 with T2DM and 300 controls)	Patients with T2DM have earlier menopause age (44.65 vs. 48.2 years, P<0.01)	Assessment of menopause age susceptible to recall bias	(206)
Khalil <i>et al</i> , 2011	2,171 patients (117 with and 2054 without diabetes mellitus)	Patients with diabetes have earlier menopause age (48.9 vs. 51.7 years, P=0.005)	No differentiation between T1DM and T2DM	(205)
Bernardi <i>et al</i> , 2017	1,654 female subjects	BMI was negatively associated with AMH (β =-0.015, 95%CI, -0.021, -0.009, P<0.0001)	Recall bias; association between obesity and AMH lacks generalizability to other racial/ethnic groups	(225)
Machtinger <i>et al</i> , 2012	Oocytes from 276 patients (105 from severely obese and 171 from normal BMI patients)	Oocytes from severely obese patients have higher incidence of double spindles (58.9 vs. 35.1%, P=0.003) and prevalence of disarranged spindles (28.6 vs. 8.6%, P=0.04)	Oocytes had been discarded and failed to fertilize, which was unclear if the results are generalizable to fertilized oocytes from the same cohort	(236)
Freeman <i>et al</i> , 2007	122 female subjects	Obese patients have lower AMH levels (geometric mean, 0.016 vs. 0.046; geometric mean ratio, 0.35, 95%CI, 0.13, 0.92, P=0.034)	AMH of postmenopausal patients was below assay threshold	(227)
Douchi <i>et al</i> , 2002	83 female patients with obesity	Patients with menstrual disorder have higher trunk-to-leg fat ratio (1.48 vs. 11.25, P<0.01)	Lack of control group of non-obese patients	(229)
Stock <i>et al</i> , 2019	80,840 female subjects	Subjects working rotating night shifts have an increased risk of earlier menopause (multivariable-adjusted HR, 1.09, 95%CI, 1.02, 1.16)	Work schedule information was not detailed	(245)

T2DM, type 2 diabetes mellitus; AMH, anti-Müllerian hormone; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

obesity, T2DM and metabolic syndrome (3,182). Moreover, involvement of the HPA and SAM axes due to mental stress is linked to increased metabolic disorder (183,184). Notably, patients with metabolic syndrome or T2DM exhibit lower OR compared with healthy counterparts (185,186), highlighting the connection between stress, metabolic disorder and ovarian function.

Abnormal glucose metabolism and insulin resistance. Previous research suggests that stressors such as stressful life events, emotional distress, anger, poor sleep and work stress disrupt glucose balance and promote insulin resistance (187). As a result, these stressors are considered independent risk factors for T2DM (188,189) and individuals experiencing

chronic stress are at a higher risk of developing T2DM compared with non-stressed individuals (190). T2DM is a chronic metabolic disorder characterized by hyperglycemia and insulin resistance, both of which may contribute to ovarian dysfunction (191,192).

As reviewed by Dri *et al* (193), granulosa, theca and stromal compartments of the ovary express insulin receptors, which bind to insulin and IGF-1, dysregulating dynamics of OR and/or impairing the survival and competence of the oocytes. Previous studies *in vitro* have demonstrated that insulin can stimulate these receptors in granulosa and theca cells, resulting in elevated levels of androgen, estrogen and progesterone (194-196). Prolonged stress and insulin resistance can lead to reduced β -cell function, necessitating exogenous

insulin administration (197). Chronic exposure to high systemic insulin levels stimulates ovarian insulin and IGF-1 receptors, resulting in follicle stimulation and increased production of ovarian androgens (198). Persistent hyperglycemia can negatively impact folliculogenesis and ovarian function, potentially via advanced glycation end-products (AGEs) and their receptors (191,199). AGEs decrease oocyte developmental competence and vascularization, induce hypoxia and decrease glucose uptake (200). Insulin resistance can also disrupt ovulation by impeding recruitment of dominant follicles, leading to anovulatory states and menstrual irregularity (201). Moreover, in T1DM, folliculogenesis, oogenesis and embryo development are impaired in mice (202), but the underlying mechanism needs to be further investigated.

Previous population studies have indicated an association between abnormal glucose metabolism, insulin resistance and ovarian function (173-180). The incidence of oligomenorrhea is notably higher in patients with T2DM compared with those with normal blood glucose levels (203,204). Additionally, Study of Women's Health Across the Nation Bone, a longitudinal and ethnically diverse research project ($n=2,171$), observed that patients with diabetes at the start of the study reached menopause ~ 3 years sooner than non-diabetic counterparts ($P=0.002$) (205). Similarly, Sekhar *et al* (206) reported that the mean age of menopause is lower in patients with T2DM (44.65 years) compared with those without T2DM (48.2 years; $P<0.01$). A retrospective cohort study by Qin *et al* (207) found that patients with T2DM had significantly decreased AMH levels (2.43 ± 2.31 vs. 3.58 ± 2.58 $\mu\text{g/l}$, $P<0.001$), and T2DM was an independent risk factor for clinical pregnancy rate (adjusted OR=0.458, adjusted 95% CI, 0.235, 0.891, $P=0.022$) and live birth rate (adjusted OR=0.227, adjusted 95% CI, 0.101, 0.513, $P<0.001$). Furthermore, early menopause (onset at <45 years of age) was found to be more prevalent among patients with T2DM compared with those without T2DM (206). Decreased estrogen secretion post-menopause can increase visceral fat deposition and insulin resistance, significantly elevating risk of T2DM (208), and hormone replacement therapy has been shown to mitigate this risk (209,210). Similarly, decreased insulin sensitivity and impaired glucose metabolism are observed in animal models that underwent ovariectomy, but these effects are reversed by chronic estrogen administration (211,212). These findings highlight the key role of estrogens in maintaining glucose homeostasis. Consequently, stress-induced impaired glucose metabolism may lead to ovarian dysfunction, which can cause further abnormal glucose metabolism.

In summary, stress-induced abnormal glucose metabolism has detrimental effects on ovarian function throughout the reproductive lifecycle. However, more animal studies and cohort studies are required to elucidate the interplay between these factors.

Obesity. Obesity has emerged as a growing health crisis with notable repercussions for public health. In recent years, accumulating evidence indicated that stress, notably increased levels of cortisol, plays a crucial role in the onset of obesity (213-216). Chronic stress activates the HPA axis, which results in elevated circulating cortisol levels. This causes the redistribution of white adipose tissue towards

the abdominal area, and also increases appetite, particularly for calorie-dense foods (217). Notably, the obesity epidemic coincides with factors such as elevated cortisol production, prolonged stress, consumption of high glycemic index foods and poor sleep quality (3). The Prospective Urban and Rural Epidemiological study involving 120,000 individuals found that participants with higher life stress scores (encompassing work, family and financial stress and major life events) exhibited a higher prevalence of abdominal obesity compared with those with lower life stress (218). Moreover, in elderly female patients, central obesity becomes common due to redistribution of adipose tissue associated with aging (219). Similar patterns observed in fat redistribution due to chronic stress and aging in female patients suggest a potential connection between these factors (220). Recent studies increasingly highlight that obesity is associated not only with stress but also with diminished ovarian function (221-223).

Population-based studies have demonstrated an inverse association between obesity and OR (186-192). A cross-sectional study on 36 healthy patients aged 40-52 years showed that AMH and inhibin levels of obese patients were reduced by 77 (0.06, 95%CI, 0.12, 0.67 vs. 0.02 ng/ml, 95%CI, 0.12, 0.67, $P=0.02$) and 24% (12.5, 95%CI, 10.1, 15.4 ng/ml vs. 9.5 ng/ml, 95% CI, 8.0, 11.3, $P=0.08$), respectively, compared with normal-weight patients after adjusting for age, body mass index (BMI), race, smoking status and alcohol use (224). In a previous study involving 1,654 African American patients aged 23-35 years, it was observed that obese participants exhibited 23.7% lower AMH concentration (2.9 vs. 3.8 ng/ml) compared with those with a BMI ≤ 25 kg/m² (225). This finding has been corroborated by several other research studies (226-228). Additionally, obesity is linked to anovulatory cycles, irregular menstrual period and, diminished implantation and pregnancy rate and it may also be associated with PCOS (229,230). Research on the effects of a high-fat diet (HFD) on ovarian follicular development has indicated a decrease in number of primordial follicles (231). Exposure to HFD results in follicular atresia, and accelerated follicle loss in rats via the activation of mTOR and the inhibition of sirtuin 1 (SIRT1) signaling, leading to premature ovarian failure (POF) (232). Previous studies on diet-induced obesity in mice reveal increased oocyte apoptosis (233), the presence of multiple spindles (double spindles) (234) and oocyte mitochondrial dysfunction such as decreased mitochondrial membrane potential, mitochondrial distribution and ATP levels (235). These findings are supported by population studies: For example, Machtinger *et al* (236) found that severe obesity is associated with a higher incidence of spindle anomalies in failed fertilized oocytes, with observations of double spindles (OR=2.68, 95%CI, 1.39-5.15, $P=0.003$) and disorganized single spindles (OR=4.58, 95%CI, 1.05-19.86, $P=0.04$). A recent study reported that an increase in BMI was negatively associated with OR measured by AMH levels in patients with PCOS ($\beta=-0.03$, 95%CI, -0.06-0.00, $P=0.034$) (237). Although direct evidence linking stress-induced obesity with impaired ovarian function is lacking, the aforementioned indirect evidence supports this connection.

Sleep disorder and decreased melatonin. Sleep disorder caused by mental stress are widely hypothesized to be associated with

infertility and ovarian dysfunction (238-240). Previous studies on animals have indicated that sleep deprivation (SD) disrupts the regularity of the estrous cycle and results in anovulation, potentially leading to reproductive dysfunction (241,242). Negative effects of SD may impede follicular development during ovarian hyperstimulation due to an increase in corticosterone levels in rats (243). SD has been shown to significantly elevate serotonin levels, which decreases estradiol production induced by FSH and FSH-driven expression of StAR protein in follicles, resulting in decreased estrogen levels in the bloodstream (244). This is also supported by population-based research: A large-scale prospective cohort study that monitored 80,840 patients from the Nurses' Health Study between 1991 and 2013 discovered that working rotating night shifts for 2 or >10 years is associated with earlier onset of menopause (245).

Melatonin secretion decreases with age, which serves a crucial role in regulating sleep and metabolic balance, with its lipophilic nature giving it potent antioxidant properties (246). Melatonin is a key player in combating aging by protecting cells from oxidative damage, a process exacerbated by the natural decline in melatonin levels over time (247,248). Previous findings linked CUS to increased ovarian ROS levels, with ROS-induced oxidative stress being a notable contributor to ovarian damage and aging (85). Previous studies have demonstrated that melatonin safeguards mouse ovarian granulosa cells by mitigating oxidative stress-induced DNA damage, mitochondrial dysfunction, lipid peroxidation and apoptosis (249), which are associated with the SIRT1/FOXO1 and FOS pathways (249-252). Moreover, melatonin improves oocyte quality by neutralizing ROS generated during follicle maturation and ovulation and fertilization via NADPH, glutathione (GSH), bone Morphogenetic Protein 15 (BMP15) and SIRT1/SOD2-associated mechanisms (253-256). On the other hand, melatonin supplements also significantly alleviated spindle/chromosome disorganization, which may involve the SIRT2-dependent H4K16 deacetylation pathway (257,258). Clinical trials have indicated that melatonin treatment in infertile patients can elevate follicular melatonin levels, reduce oxidative damage and enhance fertilization and pregnancy rates (253,257,259). Importantly, decreased melatonin secretion has been linked to a higher risk of diabetes (260), underscoring the association between melatonin levels, metabolic health and ovarian function.

6. Intervention strategies for ovarian dysfunction

Psychological intervention strategies for ovarian dysfunction. The likelihood of depression, anxiety and distress is notably high among patients experiencing infertility and psychological symptoms adversely affect fertility (261). Additionally, onset of depression often occurs before the diagnosis of POI, implying that depression and/or its treatment may contribute to development of POI (15).

The effectiveness of psychological interventions in decreasing psychological distress and association with significant increases in pregnancy rates has been shown (5). After receiving antidepressant medication and psychotherapy, infertile patients with depression have higher pregnancy rates (262). Patients with POF/POI may benefit from psychological interventions, as emotional and other menopausal symptoms

may be prolonged and not always alleviated by hormone therapy (15). Stress management and psychological therapy have been linked to spontaneous pregnancy in certain infertile couples. Multiple studies have documented cases of infertile couples conceiving naturally after adopting a child (263,264). The aforementioned data suggests that psychological interventions may be a promising approach for these individuals to enhance quality of life.

Cognitive behavioral therapy (CBT). CBT can help patients alleviate stress and achieve relaxation by identifying and analyzing problems, recognizing unproductive thoughts and behaviors, creating and implementing replacement thoughts and behaviors, regular review and adjustment of strategies, and applying learned skills to daily life (265). CBT has been demonstrated to be an effective approach in treating depressive disorder, with meta-analyses of randomized controlled trials corroborating its efficacy for both anxiety (266-268) and depression (269,270).

A randomized controlled trial involving 56 pregnant patients with a history of primary infertility indicated that CBT counseling alleviates perceived stress, and anxiety, as well as enhancing the quality of life score (271). Domar *et al* (272) showed that infertile patients assigned to either structured CBT or standard support groups had a higher pregnancy rate (52 vs. 20%, $P=0.05$), compared with those who did not participate in these programs during their second IVF cycle; however, P -value decreased slightly to 0.038 after adjusting for intracytoplasmic sperm injection (ICSI) through logistic regression. Mean stress scores after CBT treatment in infertile patients were significantly decreased compared with before (2.7 ± 0.62 vs. 3.5 ± 0.62 ; $P<0.05$) (273), which was confirmed by a previous web-based CBT study (274). Researchers have identified CBT as an effective treatment for enhancing the quality of life (vasomotor symptoms, physical, psychosocial, sexual and total domain) of perimenopausal patients (275-280). A randomized controlled trial conducted with 50 patients with POI revealed mean scores of stress [adjusted mean difference (AMD), -10.97; 95%CI, -11.64, -10.29; $P<0.001$], state anxiety (AMD, -14.76; 95%CI, -15.77, -13.74; $P<0.001$), trait anxiety (AMD, -14.41; 95%CI, -15.47, -13.74; $P<0.001$) and depression (AMD, -7.44; 95%CI, -8.41, -6.46; $P<0.001$) were significantly lower in the CBT group compared with control group receiving routine care (281), suggesting healthcare providers should employ this method to enhance mental health in these patients.

A study allocated 16 patients with FHA equally to CBT group or an observation group for 20 weeks; 6/8 patients in the CBT group experienced recovery of ovarian activity compared with 2/88 in the observation group (87.5 vs. 25.0%, $\chi^2=7.14$) (282). Besides promoting ovulation, CBT has also been shown to lower cortisol levels in patients with FHA (283). CBT not only reinstates ovarian function but also impacts metabolic processes (284). A pilot study on 12 adolescents with PCOS demonstrated that CBT notably decreases weight (104 ± 26 vs. 93 ± 18 kg, $P<0.05$) and improves depression score (17 ± 3 vs. 9.6 ± 2 , $P<0.01$) (285). Another study involving 15 overweight/obese adolescents with PCOS revealed that weekly CBT + lifestyle modification sessions (LS) for 8 weeks significantly led to weight loss, enhanced quality of life and reduced depressive symptoms compared with those only receiving LS intervention (286).

Mindfulness-based stress reduction (MBSR). MBSR, a strategy of lessening stress and anxiety through meditation, breathwork and body awareness, is a methodical mindfulness meditation plan that is progressively accessible in medical and healthcare environments to boost mental health and general wellbeing (287). MBSR has been demonstrated to decrease mental suffering and enhance life quality in patients with cancer, heart disease and depressions (288,289).

Individuals diagnosed with POF or POI often experience prolonged mood disturbance and other menopausal symptoms that may not be effectively alleviated by hormone therapy (15), indicating that MBSR may offer potential benefits. A randomized controlled trial including 197 symptomatic peri- and postmenopausal patients found that both MBSR and menopause education control (MEC) decreases total Greene Climacteric Scale score and symptom score reduction of anxiety and depression is significant in the MBSR compared with the MEC group (anxiety, 5.97 ± 2.49 vs. 6.97 ± 2.57 , $P=0.07$; depression, 4.78 ± 2.60 vs. 5.39 ± 2.41 , $P=0.031$) (290). In patients with POI, mindfulness practices have been shown to decrease scores of menopause-specific quality of life (compared with baseline, 48.32 ± 4.96 vs. 95.6 ± 9.77 , $P<0.0001$; compared with control, 48.32 ± 4.96 vs. 102.6 ± 14.9 , $P<0.0001$) and the frequency of hot flushes (6.74 ± 6.34 vs. 23.4 ± 13.9 , $P<0.0001$) (291). MBSR improves emotional wellbeing and biological outcomes in infertile patients (292-294).

Music therapy. Previous research has shown that music therapy has the potential to decrease stress, improve quality of life and alleviate depression and anxiety (295). In a randomized-controlled study of 48 postmenopausal patients, music therapy significantly decreased BDI score (11.81 ± 8.62 vs. 16.44 ± 6.09 , $P=0.031$) compared with control and the Menopause Rating Scale (MRS) total and sub-scale scores were significantly decreased when comparing before and after intervention (296).

In a study of 40 patients with perimenopause syndrome, music therapy was more likely to improve psychological and emotional symptoms compared with CBT (MRS total, 9.2 vs. 3.5, $P=0.008$; MRS-psychological, 6.5 vs. 0.9, $P=0.004$; Patient Health Questionnaire 9 score, 4.3 vs. 1.6, $P=0.009$) (297). A comprehensive meta-analysis indicated that music therapy decreases the anxiety (MD=-3.09, 95%CI, -5.57, -0.61, $P=0.01$) and pain score (MD=-2.93, 95%CI, -3.86, -2.00, $P<0.0001$) and increased the satisfaction score (MD=1.51, 95%CI, 0.40, 2.61, $P=0.008$) in infertile patients undergoing ART (298). While music therapy increases the clinical pregnancy rates, the difference is not statistically significant (RR=1.08, 95%CI, 0.94, 1.26, $P=0.28$) (298,299).

Other methods to manage stress. Alongside seeking advice from professional psychologists, individuals may opt for self-care. An evaluation of 166 patients undergoing first-time IVF through a randomized controlled prospective study, examining the effectiveness of a cognitive coping and relaxation intervention (CCRI) that could be self-administered indicated that patients who engaged in the CCRI demonstrated enhanced positive reappraisal coping, better Fertility Quality of Life score and reduced levels of anxiety (300). Another randomized controlled prospective pilot study explored the

impact of an online version of the mind/body program (301), where patients assigned to the intervention group showed significant decreases in anxiety and depression, along with an increased likelihood of pregnancy.

Yoga has been shown to be a beneficial intervention for anxiety and depression, stress reduction and enhancement of the overall wellbeing among the general public (302). Furthermore, yoga can alleviate anxiety and depression in individuals undergoing IVF treatment and increase the ART success rate (303). Yoga can enhance the quality of life in relation to infertility, with a specific focus on diminishing adverse emotions and cognition linked to infertility (304). A separate study investigating yoga as a complementary approach for patients receiving IVF treatment yielded comparable results (305). Yoga alleviates the menopausal symptoms, anxiety and depression of menopausal patients and decreases the levels of FSH and LH (306,307).

Frederiksen *et al* (308) assessed advantages of expressive writing for individuals with from infertility; male and female patients exhibited a noticeable decrease in depressive symptoms. In addition, adhering to a balanced diet, leading a healthy lifestyle and managing work-life balance are potential strategies to alleviate stress and safeguard ovarian function (309).

Metabolic interventions for ovarian dysfunction. As aforementioned, the activation of stress-associated neuroendocrine systems causes metabolic imbalance in the body, and metabolic disorders lead to ovary dysfunction.

Caloric restriction (CR). CR refers to a reduction in calorie consumption without eliminating essential nutrients (310). CR is hypothesized to extend the lifespan of rodents, yeast, worms, flies and primates by decreasing body weight and slowing aging process (311). CR has been shown to mitigate age-associated diseases such as neurodegeneration, hepatic steatosis and T2DM (312).

Notably, recent studies have shown that CR can protect ovarian function. CR decreases aneuploidy, chromosomal misalignment and meiotic spindle abnormality in oocytes in aged mice (313-315). CR can attenuate aging-associated decrease in chromosomal cohesion and protect the normal progress of meiosis (315). CR enhances ovarian estrogen sensitivity and inhibits ovulation, thereby extending reproductive lifespan (316,317). CR can also reduce primordial follicle activation and lead to increased ovarian Forkhead box O3 (Foxo3a) expression, activation of the SIRT1 signaling pathway and suppression of the mTOR signaling pathway, which may increase preservation of the ovarian primordial follicular reserve and delay menopause onset (318-322).

Obesity impairs ovarian function and obese patients are often encouraged to lose weight before conception to increase the chances of a successful pregnancy (323). However, the protective effect of CR on ovarian function lacks large-scale multicenter clinical trials and CR is a long-term dietary adjustment process that is difficult to maintain (324). Recently, there has been considerable interest in identifying drugs that can mimic the effects of CR. CR mimetics (CRMs) promote lifespan and sustain the health benefits of CR without requiring dietary restriction (325-329). CRMs have good clinical prospects because they do not require long-term dietary restriction and have better patient compliance.

Metformin. Metformin is a widely prescribed medication for management of T2DM (330) that reduces blood glucose by decreasing glucose absorption, enhancing peripheral glucose uptake and increasing insulin sensitivity (331). Metformin can decrease the risk of all-cause mortality and cardiovascular death in patients with T2DM (332). Moreover, metformin is also known for anti-aging (333) and anticancer (334) effects.

Metformin has been demonstrated to increase OR and protect ovarian function through regulatory mechanisms such as inhibiting the mTOR pathway, enhancing SIRT1 expression and decreasing oxidative stress damage (335,336). Furthermore, in aged mice, metformin decreases mitochondrial ROS via SIRT3-mediated acetylation of SOD2K68 in oocytes (337). For chemotherapy-induced ovarian damage, metformin may attenuate carboplatin-induced ovarian damage, potentially through its antioxidative effects (338). In addition, metformin decreases aging-related ovarian fibrosis. Metformin-responsive macrophage subpopulations appear in aged mice treated with metformin, which may decrease ovarian fibrosis by clearing fibroblasts that produce the senescence-associated secretory phenotype in aged ovaries (339). Therefore, metformin may serve as a promising drug to protect reproductive function.

Resveratrol. Resveratrol is a derivative of stilbene produced by >70 species of plants (340) in response to external adverse stimuli. Resveratrol has multiple protective effects in mammal models of T2DM, metabolic syndrome, cancer and neurodegenerative and cardiovascular diseases (341). For example, resveratrol increases SIRT1 levels and improves insulin resistance in a HFD rat model, indicating resveratrol has the potential to combat insulin resistance and maintain glucose metabolism homeostasis (342). Furthermore, resveratrol induces a CR-like transcriptional signature in mice and mimics metabolic changes of human CR (343).

In humans, resveratrol can improve the follicular micro-environment to improve IVF outcomes (344). Intraperitoneal injection of resveratrol during superovulation improves oocyte quality in both young and old mice, and increased the number of oocytes retrieved from old mice (345). Resveratrol improves fertility of reproductive age female mice, which may be achieved by activating SIRT1 and increasing the expression of Foxo3a (346-349). *In vitro*, resveratrol increased first polar body emission rates and improves oocyte mitochondrial function (350-352). *In vitro*, resveratrol protects granulosa cells by activating autophagy to resist oxidative stress (353,354). In conclusion, resveratrol is beneficial to ovarian function and protects oocytes.

7. Conclusion

Psychological stress is associated with poor health and impaired ovarian function (2,4). The present review summarizes the adverse effects of mental stress on ovarian function, which are associated with decreased IVF success rates and OR and the occurrence of POI, FHA and PCOS. Mental stress is involved in the pathogenesis of POI, FHA and PCOS (15,17,61). However, more prospective studies are needed to explore the effect of psychological stress in initiation and progression of these diseases. Elevated levels of perceived stress, as well as SAA, could reduce OR (13,56,58). However, salivary cortisol,

another biomarker used to measure psychological stress, has no association with fecundability (181). Cortisol exhibits a distinct circadian rhythm, with peak levels occurring in the morning and decreasing throughout the day; thus, it may be important to obtain multiple samples/day from a patient in order to investigate its effects on human health (355). Mental stress has an adverse effect on the outcome of IVF or ICSI, although some studies suggest that there is no association between them (48). To the best of our knowledge, no studies have reported that psychological stress has a positive effect on pregnancy outcomes. Anderheim *et al* (48) found no evidence that mental stress impairs IVF outcomes. However, Aimagambetova *et al* (36) found that higher STAI-S and STAI-T are negatively associated with clinical pregnancy outcomes. A potential reason for this discrepancy is that, when filling out psychological questionnaires, patients may not provide accurate assessments of distress. Different inclusion criteria, assessment tools for psychological status and study design may be additional reasons for the inconsistent results. The influence of stress on ART outcomes remains controversial, but, for infertile patients, psychological intervention can alleviate anxiety and depression, potentially resulting in notably improved pregnancy rates. Multi-center clinical trials with large sample sizes are necessary in future research. Under ideal conditions, prospective studies through puberty to perimenopause should regularly collect psychological questionnaires/scales, metabolic and ovarian function indexes to demonstrate causal mechanisms linking stress and ovarian dysfunction.

The present study summarizes animal models used to study the impact of mental stress on ovarian function, such as CUS, CRS and chronic cold stress, as well as evaluation methods. Mental stress affects the follicle and ovarian vascular function via the HPA, SAM and HPO axis and neurometabolic network, in which stress induces granulosa cell apoptosis by activating the MAPK, FAS and TNF- α pathway and increasing ROS, leading to overactivation of primordial follicles and decreasing the number of follicles by activating the PI3K/AKT pathway, as well as oocyte quality by downregulating BDNF, GDF9 and CCNB1, inhibiting the cAMP pathway, mitochondrial energy metabolism imbalance and inducing ROS accumulation. In addition, stress can lead to disorder of ovarian vascular structure and microenvironment by upregulating expression of ET-1 and ET-AR and downregulating expression of ET-BR, leading to a decline in ovarian function (Fig. 4).

Multiple studies have examined the impact of chronic stress on the neuroendocrine system over extended periods (156,356). In the existing studies, traditional biological stress markers (cortisol and α -amylase) have been widely used to assess stress levels of patients and experimental animals (10,58,85,181). However, due to the differences in susceptibility between individuals and evaluation methods, previous results are inconsistent. Obayashi (357) summarized advantages and weaknesses of different salivary stress markers in the assessment of stress, such as cortisol, α -amylase, chromogranin A and IgA and proposed optimization of the method of saliva collection in order to improve the consistency of stress levels. As Shah *et al* (358) noted, when exploring the association between psychological stress and ovarian function, a comprehensive assessment of stress levels should include physiological

markers (such as heart rate variability, blood pressure and cytokine levels) and biochemical indicators (cortisol, catecholamines, copeptin, SAA, IL-6 and C-reactive protein levels), as well as individual subjective assessments (self-reported stress levels, perceived stress scale or psychometric evaluations). Neuroendocrine changes caused by mental stress lead to systemic inflammation, leading to an increase in systemic inflammatory markers and health issues such as cardiovascular disease, cognitive dysfunction and accelerated aging (359). Therefore, inflammatory biomarkers such as TNF- α , HIF-1 α and asymmetric dimethylarginine (ADMA) may serve as biological indicators to measure mental stress and its impact on physical health. Combinations of different markers and approaches such as wearable device-based stress detection (360) may establish effective stress markers. However, its effects need more clinical research for verification.

Existing studies focus on the direct role of psychological stress on the onset of POI, FHA and PCOS (15,17,61). For example, most studies have explored the impact of PCOS on the mental stress or psychological-associated disease (361-363). Large-scale prospective studies with larger samples are needed to support whether mental stress causes PCOS. Furthermore, the existing evidence that mental stress impairs ovarian function through metabolic disturbances is indirect (207,236). cohort studies and animal experiments are required to determine whether mental stress directly affects ovarian function through metabolism-related diseases.

It is key to elucidate the specific molecular mechanism underlying the effect of on the ovary and provide psychological intervention strategies for patients with ovarian dysfunction, especially for those in need of ART intervention. Hence, psychological interventions (CBT, MBSR and music therapy) may be beneficial to reduce adverse influence of stress and improve ovarian function and reproductive outcomes. The present review may provide an alternative intervention strategy for improvement of ovarian dysfunction and infertility.

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Authors' contributions

YL and FF conceived and designed the study. YH and FF wrote the manuscript and constructed figures and tables. WuW, WM, WeW, WR and SW revised the manuscript. All the authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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