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

YU HU[1-3], WUYANG WANG[1-3], WENQING MA[1-3], WENWEN WANG[1-3], WU REN[1-3], SHIXUAN WANG[1-3], FANGFANG FU[1-3] and YAN LI[1-3]

[1]Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China; [2]National Clinical Research Center for Obstetrical and Gynecological Diseases, Wuhan, Hubei 430030, P.R. China; [3]Ministry of Education, Key Laboratory of Cancer Invasion and Metastasis, Wuhan, Hubei 430030, P.R. China

Received August 6, 2024; Accepted November 18, 2024

DOI: 10.3892/ijmm.2024.5475

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.

Correspondence to: Dr Fangfang Fu or Professor Yan Li, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, P.R. China
E-mail: fufangfang@tjh.tjmu.edu.cn
E-mail: liyan@tjh.tjmu.edu.cn

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

Contents

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%)

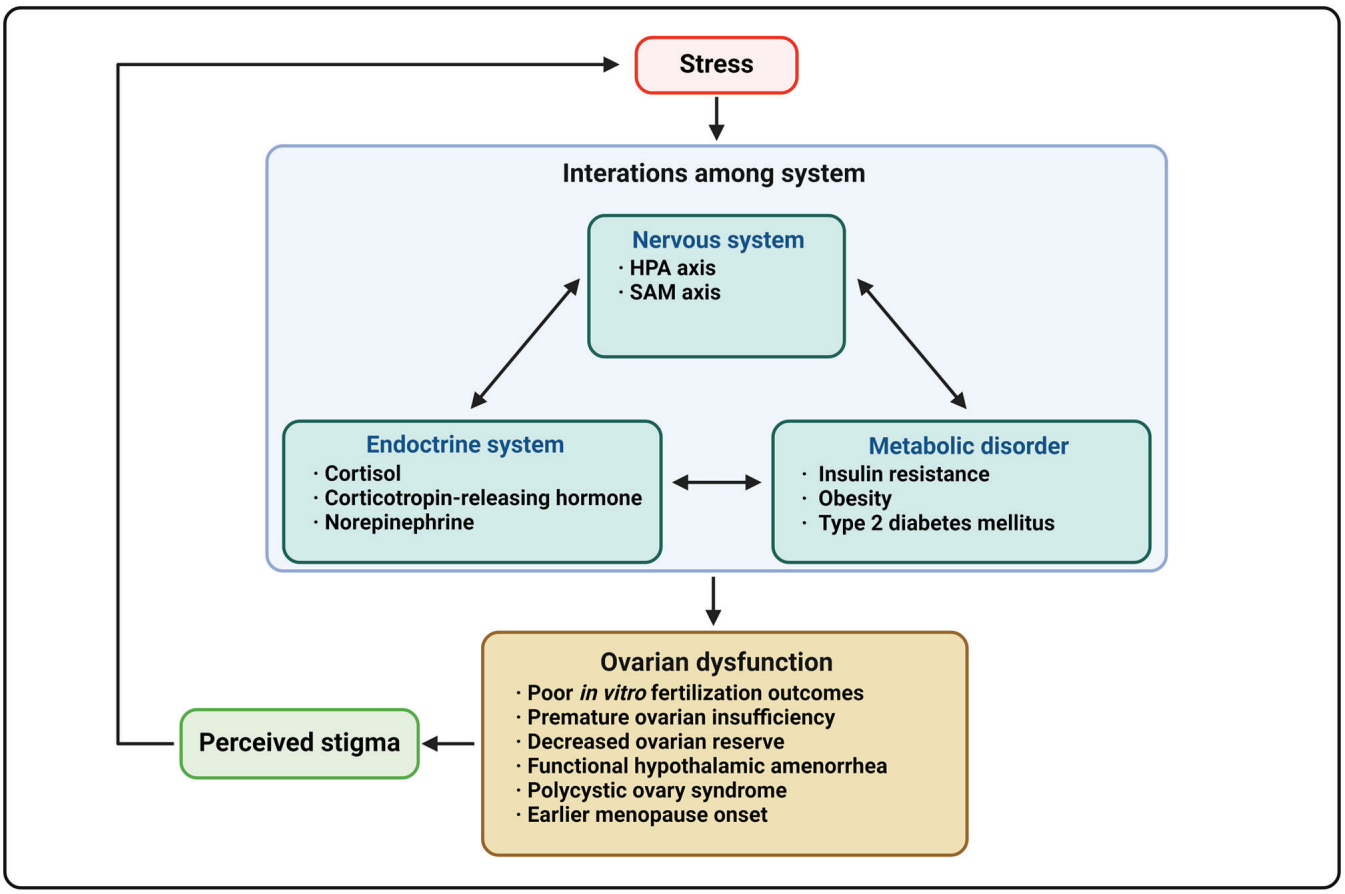

Figure 1. Association between elevated psychological stress and diminished ovarian function. Mental stress triggers the interaction between the nervous and the endocrine system, leading to metabolic disorder. These elements interact with each other, creating a NEM network that results in impaired ovarian 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 *et al*, 2023	110 infertile patients; 112 controls	No association between serum cortisol levels and IVF cycles (τ=0.071, P≥0.05) and clinical pregnancy (τ=-0.047, P≥0.05).	Cortisol may be influenced by other factors	(42)
Mirzaasgari *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 2016	217 couples undergoing ICSI	Patients with positive pregnancy outcome had lower depression score (P<0.05)	Small sample size	(35)
Lynch *et al*, 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 *et al*, 2014	52 patients undergoing IVF	No association between urine cortisol and clinical pregnancy (β=-0.18, 95%CI, -0.04, 0.02, P=0.48).	Small sample size; single time point of uterine sample collection	(50)
An *et al*, 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 *et al*, 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 *et al*, 2013	89 patients undergoing IVF and 77 partners	Partner composite psychological distress score was a predictor of fertilization rate (β=-0.18, SE=0.09, P=0.049).	Single time point of psychological assessment	(38)
Pasch *et al*, 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 *et al*, 2012	339 patients trying to conceive	No association between baseline psychosocial and pregnancy rate	Response bias; short follow-up period	(47)
Li *et al*, 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 *et al*, 2005	166 patients undergoing IVF	No difference in psychological effects between patients with or without adverse pregnancy outcomes	Response bias	(48)
Klonoff-Cohen *et al*, 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 *et al*, 2000	22 infertile patients	Patients with negative IVF outcome had higher state anxiety level (P<0.06).	Small sample size	(39)
Milad *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 2012	979 patients aged 25-45 years	Higher stress levels are associated with higher AFC (β=0.545, P=0.005) and accelerated follicle loss	Single time point of AFC assessment	(56)
Bleil *et al*, 2012	683 patients aged 25-45 years	Psychological stress accelerates AFC decline in patients with low (β=-0.070, P=0.021) but not high positive affect (β=0.018, P=0.54)	Response bias; unrepresentative population sample	(57)

D, FHA

First author (year)	Subjects	Results	Limitations	(Refs.)
Dundon *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 (β=0.545, P=0.005), and stress accelerates age-related AFC decline (β=-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 (β=-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).

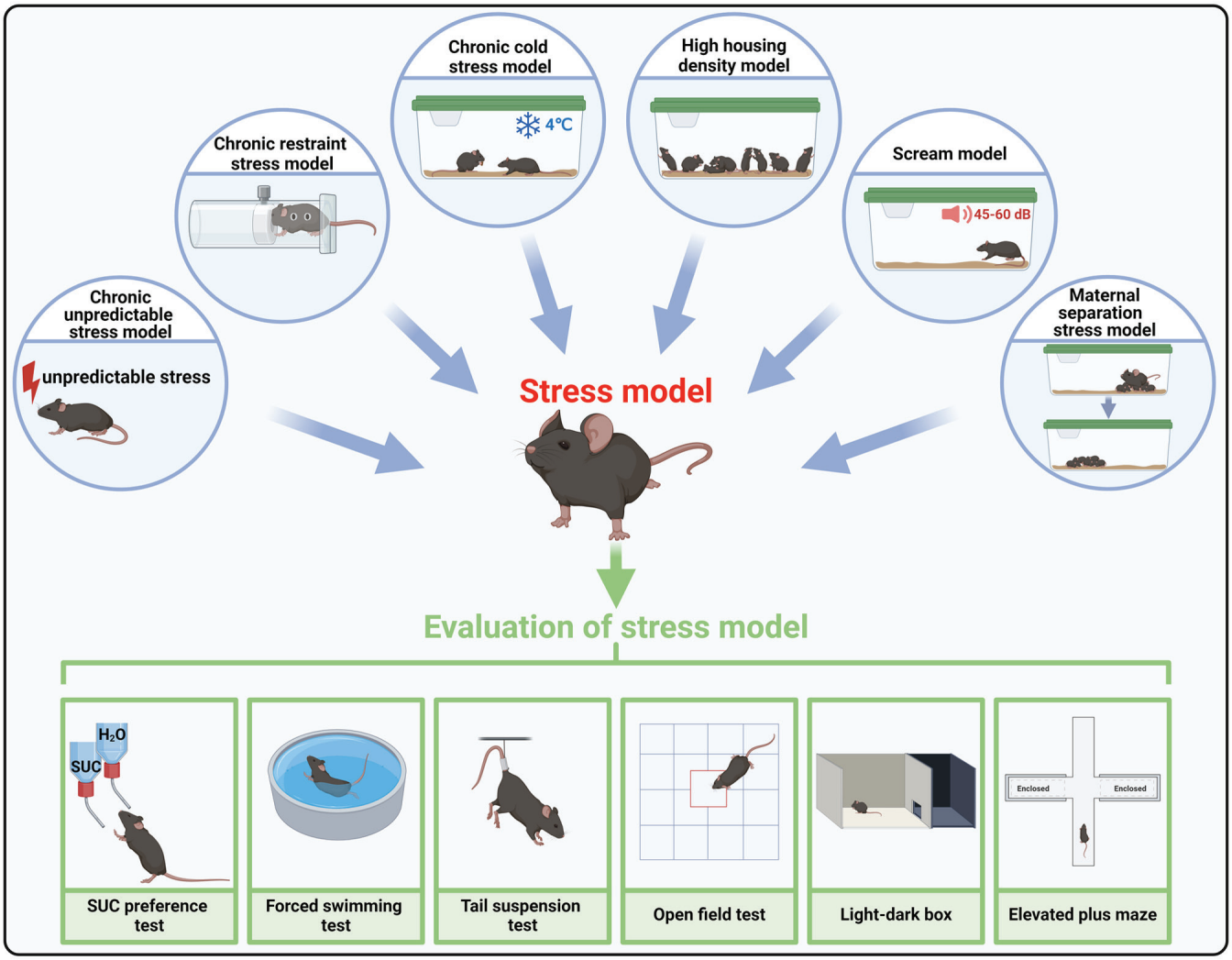

Figure 2. Models used in stress-associated ovarian function studies and stress assessment methods. Chronic unpredictable stress and chronic restraint stress models are the most widely used. The cold stress model is primarily applied to examine sympathetic-adrenal-medullary activation effects on the ovary. 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 downregulation 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 cm^2 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 adrenocorticotropic 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

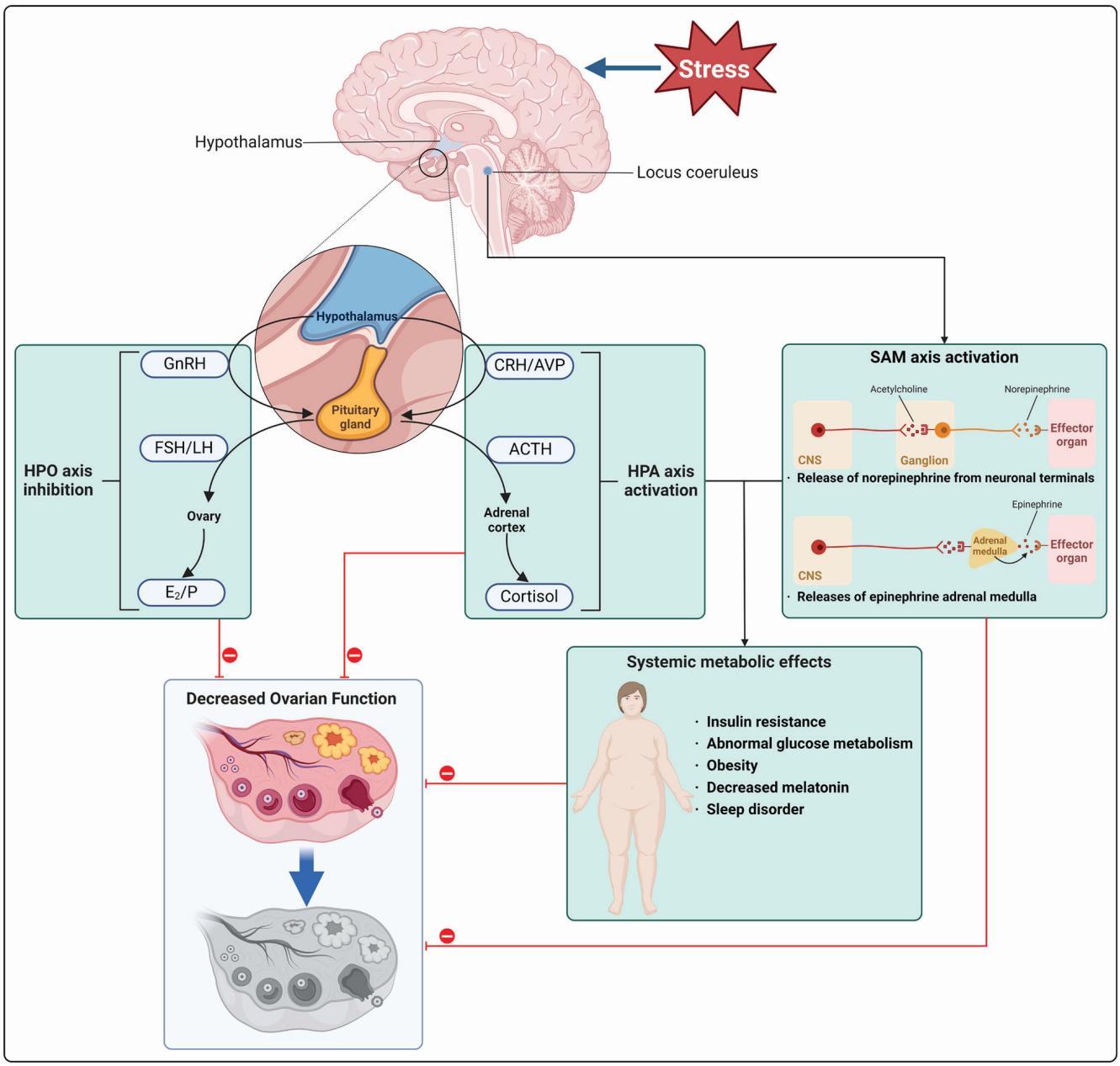

Figure 3. Association between psychological stress, HPA, HPO and SAM axes and metabolic disorder in regulating ovarian function. Psychological stress leads to the activation of the HPA and SAM axes, while concurrently suppressing the HPO axes. In response to stress, activation of the paraventricular nucleus region 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; E_2, 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 (β=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

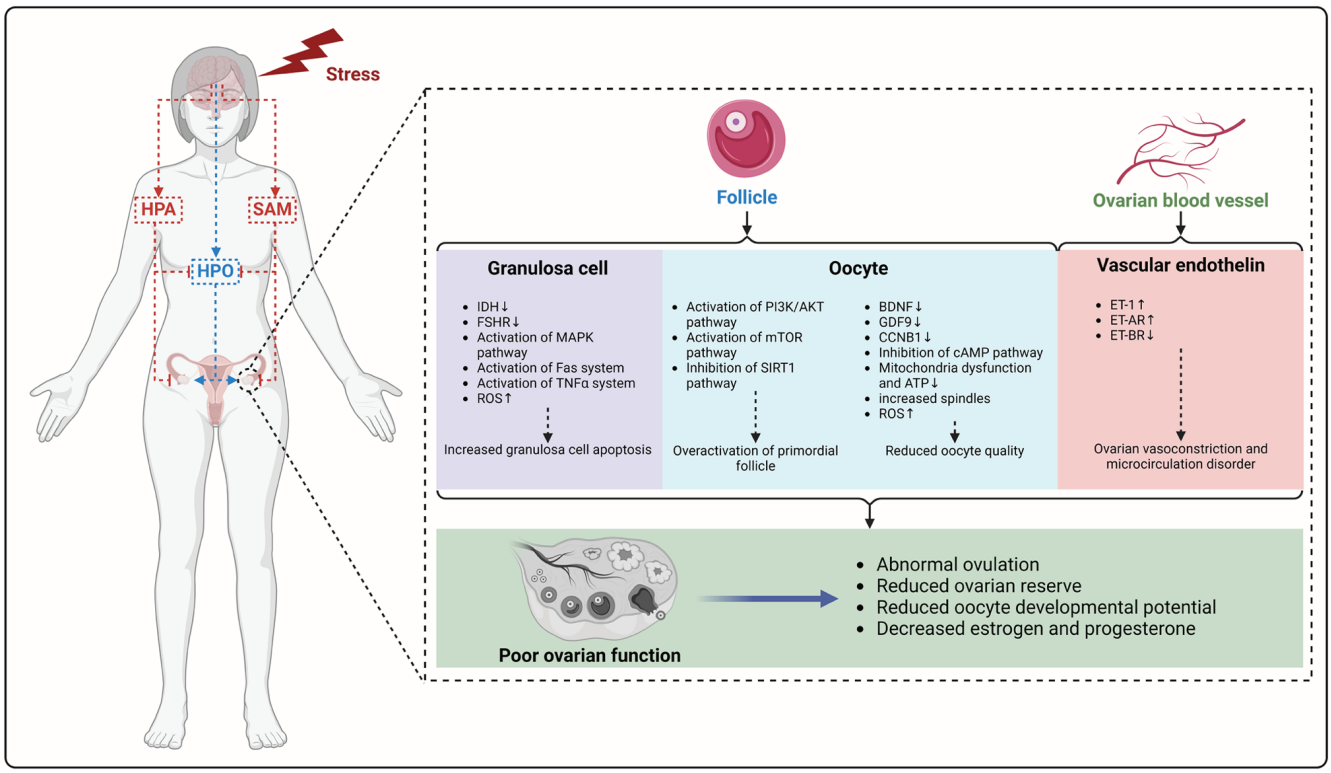

Figure 4. Mechanisms of ovarian dysfunction caused by stress. Psychological stress affects ovarian function and inhibits the HPO axis by activating the HPA and SAM axes. This causes increased granulosa cell apoptosis, diminished oocyte quality and excessive activation of primordial follicles, culminating 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 TNFα 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 BDNFl increased apoptosis	(128,161)
	N/A	Rats	NE	Activation of TGFβ-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; TGFβ, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 μg/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/m^2 (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 (β=-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%, χ^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 microenvironment 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 POCS (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-1α 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 lager 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.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Key Research and Development Program of China (grant nos. 2022YFC2704100 and 2021YFC2700402-02) and National Natural Science Foundation of China (grant no. 81902669).

Availability of data and materials

Not applicable.

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.

References

1. Wang S, Quan L, Chavarro JE, Slopen N, Kubzansky LD, Koenen KC, Kang JH, Weisskopf MG, Branch-Elliman W and Roberts AL: Associations of depression, anxiety, worry, perceived stress, and loneliness prior to infection with risk of post-COVID-19 conditions. JAMA Psychiatry 79: 1081-1091, 2022.
2. Valsamakis G, Chrousos G and Mastorakos G: Stress, female reproduction and pregnancy. Psychoneuroendocrinology 100: 48-57, 2019.
3. Kivimäki M, Bartolomucci A and Kawachi I: The multiple roles of life stress in metabolic disorders. Nat Rev Endocrinol 19: 10-27, 2023.
4. Bala R, Singh V, Rajender S and Singh K: Environment, lifestyle, and female infertility. Reprod Sci 28: 617-638, 2021.
5. Rooney KL and Domar AD: The relationship between stress and infertility. Dialogues Clin Neurosci 20: 41-47, 2018.
6. Maeda E, Nomura K, Hiraike O, Sugimori H, Kinoshita A and Osuga Y: Domestic work stress and self-rated psychological health among women: A cross-sectional study in Japan. Environ Health Prev Med 24: 75, 2019.
7. Liu Y and Aungsuroch Y: Work stress, perceived social support, self-efficacy and burnout among Chinese registered nurses. J Nurs Manag 27: 1445-1453, 2019.
8. Bapayeva G, Aimagambetova G, Issanov A, Terzic S, Ukybassova T, Aldiyarova A, Utepova G, Daribay Z, Bekbossinova G, Balykov A, *et al*: The effect of stress, anxiety and depression on in vitro fertilization outcome in kazakhstani public clinical setting: A cross-sectional study. J Clin Med 10: 937, 2021.
9. Xu H, Ouyang N, Li R, Tuo P, Mai M and Wang W: The effects of anxiety and depression on in vitro fertilisation outcomes of infertile Chinese women. Psychol Health Med 22: 37-43, 2017.
10. Sallem A, Essoussi H, Mustapha HB, Zaouali M and Ajina M: Impact of psychological stress on the outcomes of assisted reproduction in Tunisian infertile women. Pan Afr Med J 40: 250, 2021.
11. Klonoff-Cohen H, Chu E, Natarajan L and Sieber W: A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril 76: 675-687, 2001.
12. Buck Louis GM, Lum KJ, Sundaram R, Chen Z, Kim S, Lynch CD, Schisterman EF and Pyper C: Stress reduces conception probabilities across the fertile window: Evidence in support of relaxation. Fertil Steril 95: 2184-2189, 2011.
13. Mínguez-Alarcón L, Williams PL, Souter I, Ford JB, Hauser R and Chavarro JE; Earth Study Team: Perceived stress and markers of ovarian reserve among subfertile women. Reprod Biomed Online 46: 956-964, 2023.
14. Golenbock SW, Wise LA, Lambert-Messerlian GM, Eklund EE and Harlow BL: Association between a history of depression and anti-müllerian hormone among late-reproductive aged women: The Harvard study of moods and cycles. Womens Midlife Health 6: 9, 2020.
15. Allshouse AA, Semple AL and Santoro NF: Evidence for prolonged and unique amenorrhea-related symptoms in women with premature ovarian failure/primary ovarian insufficiency. Menopause 22: 166-174, 2015.
16. Lawson EA, Donoho D, Miller KK, Misra M, Meenaghan E, Lydecker J, Wexler T, Herzog DB and Klibanski A: Hypercortisolemia is associated with severity of bone loss and depression in hypothalamic amenorrhea and anorexia nervosa. J Clin Endocrinol Metab 94: 4710-4716, 2009.

17. Goodarzi MO, Dumesic DA, Chazenbalk G and Azziz R: Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 7: 219-231, 2011.
18. Freeman EW, Sammel MD, Lin H and Nelson DB: Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 63: 375-382, 2006.
19. Gao L, Zhao F, Zhang Y, Wang W and Cao Q: Diminished ovarian reserve induced by chronic unpredictable stress in C57BL/6 mice. Gynecol Endocrinol 36: 49-54, 2020.
20. Jiang Y, Xu J, Tao C, Lin Y, Lin X, Li K, Liu Q, Saiyin H, Hu S, Yao G, *et al*: Chronic stress induces meiotic arrest failure and ovarian reserve decline via the cAMP signaling pathway. Front Endocrinol (Lausanne) 14: 1177061, 2023.
21. Xu M, Sun J, Wang Q, Zhang Q, Wei C and Lai D: Chronic restraint stress induces excessive activation of primordial follicles in mice ovaries. PLoS One 13: e0194894, 2018.
22. Poole L and Hackett RA: Diabetes distress: The psychological burden of living with diabetes. Lancet Diabetes Endocrinol 12: 439-441, 2024.
23. Bartoskova Polcrova A, Dalecka A, Szabo D, Gonzalez Rivas JP, Bobak M and Pikhart H: Social and environmental stressors of cardiometabolic health. Sci Rep 14: 14179, 2024.
24. Schliep KC, Mumford SL, Vladutiu CJ, Ahrens KA, Perkins NJ, Sjaarda LA, Kissell KA, Prasad A, Wactawski-Wende J and Schisterman EF: Perceived stress, reproductive hormones, and ovulatory function: A prospective cohort study. Epidemiology 26: 177-184, 2015.
25. Harlow BL, Wise LA, Otto MW, Soares CN and Cohen LS: Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: The Harvard study of moods and cycles. Arch Gen Psychiatry 60: 29-36, 2003.
26. Albert KM and Newhouse PA: Estrogen, stress, and depression: cognitive and biological interactions. Annu Rev Clin Psychol 15: 399-423, 2019.
27. Yatsenko SA and Rajkovic A: Genetics of human female infertility. Biol Reprod 101: 549-566, 2019.
28. Matthiesen SMS, Frederiksen Y, Ingerslev HJ and Zachariae R: Stress, distress and outcome of assisted reproductive technology (ART): A meta-analysis. Hum Reprod 26: 2763-2776, 2011.
29. Massey AJ, Campbell B, Raine-Fenning N, Aujla N and Vedhara K: The association of physiological cortisol and IVF treatment outcomes: A systematic review. Reprod Med Biol 13: 161-176, 2014.
30. Chen TH, Chang SP, Tsai CF and Juang KD: Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 19: 2313-2318, 2004.
31. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist O and Sundström Poromaa I: Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod 23: 2056-2063, 2008.
32. Pasch LA, Holley SR, Bleil ME, Shehab D, Katz PP and Adler NE: Addressing the needs of fertility treatment patients and their partners: Are they informed of and do they receive mental health services? Fertil Steril 106: 209-215.e2, 2016.
33. Lakatos E, Szigeti JF, Ujma PP, Sexty R and Balog P: Anxiety and depression among infertile women: A cross-sectional survey from Hungary. BMC Womens Health 17: 48, 2017.
34. An Y, Sun Z, Li L, Zhang Y and Ji H: Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: Psychological and neurohormonal assessment. J Assist Reprod Genet 30: 35-41, 2013.
35. Terzioglu F, Turk R, Yucel C, Dilbaz S, Cinar O and Karahalil B: The effect of anxiety and depression scores of couples who underwent assisted reproductive techniques on the pregnancy outcomes. Afr Health Sci 16: 441-450, 2016.
36. Aimagambetova G, Issanov A, Terzic S, Bapayeva G, Ukybassova T, Baikoshkarova S, Aldiyarova A, Shauyen F and Terzic M: The effect of psychological distress on IVF outcomes: Reality or speculations? PLoS One 15: e0242024, 2020.
37. Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB and Westphal LM: Stress and anxiety scores in first and repeat IVF cycles: A pilot study. PLoS One 8: e63743, 2013.
38. Quant HS, Zapantis A, Nihsen M, Bevilacqua K, Jindal S and Pal L: Reproductive implications of psychological distress for couples undergoing IVF. J Assist Reprod Genet 30: 1451-1458, 2013.
39. Csemiczky G, Landgren BM and Collins A: The influence of stress and state anxiety on the outcome of IVF-treatment: Psychological and endocrinological assessment of Swedish women entering IVF-treatment: Stress and state anxiety on outcome of IVF-treatment. Acta Obstet Gynecol Scand 79: 113-118, 2000.
40. Boivin J, Griffiths E and Venetis CA: Emotional distress in infertile women and failure of assisted reproductive technologies: Meta-analysis of prospective psychosocial studies. BMJ 342: d223, 2011.
41. Pasch LA, Gregorich SE, Katz PK, Millstein SG, Nachtigall RD, Bleil ME and Adler NE: Psychological distress and in vitro fertilization outcome. Fertil Steril 98: 459-464, 2012.
42. Chai Y, Li Q, Wang Y, Niu B, Chen H, Fan T, Ke X and Zou H: Cortisol dysregulation in anxiety infertile women and the influence on IVF treatment outcome. Front Endocrinol (Lausanne) 14: 1107765, 2023.
43. Cesta CE, Johansson ALV, Hreinsson J, Rodriguez-Wallberg KA, Olofsson JI, Holte J, Wramsby H, Wramsby M, Cnattingius S, Skalkidou A and Nyman Iliadou A: A prospective investigation of perceived stress, infertility-related stress, and cortisol levels in women undergoing in vitro fertilization: Influence on embryo quality and clinical pregnancy rate. Acta Obstet Gynecol Scand 97: 258-268, 2018.
44. Mirzaasgari H, Momeni F, Pourshahbaz A, Keshavarzi F and Hatami M: The relationship between coping strategies and infertility self-efficacy with pregnancy outcomes of women undergoing in vitro fertilization: A prospective cohort study. Int J Reprod Biomed 20: 539-548, 2022.
45. Peng M, Wen M, Jiang T, Jiang Y, Lv H, Chen T, Ling X, Li H, Meng Q, Huang B, *et al*: Stress, anxiety, and depression in infertile couples are not associated with a first IVF or ICSI treatment outcome. BMC Pregnancy Childbirth 21: 725, 2021.
46. Park J, Stanford JB, Porucznik CA, Christensen K and Schliep KC: Daily perceived stress and time to pregnancy: A prospective cohort study of women trying to conceive. Psychoneuroendocrinology 110: 104446, 2019.
47. Lynch CD, Sundaram R, Buck Louis GM, Lum KJ and Pyper C: Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity? Fertil Steril 98: 453-458, 2012.
48. Anderheim L, Holter H, Bergh C and Möller A: Does psychological stress affect the outcome of in vitro fertilization? Hum Reprod 20: 2969-2975, 2005.
49. Milad MP, Klock SC, Moses S and Chatterton R: Stress and anxiety do not result in pregnancy wastage. Hum Reprod 13: 2296-2300, 1998.
50. Butts CD, Bloom MS, Frye CA, Walf AA, Parsons PJ, Steuerwald AJ, Ilonze C and Fujimoto VY: Urine cortisol concentration as a biomarker of stress is unrelated to IVF outcomes in women and men. J Assist Reprod Genet 31: 1647-1653, 2014.
51. Stuenkel CA and Gompel A: Primary ovarian insufficiency. N Engl J Med 388: 154-163, 2023.
52. Sun J, Fan Y, Guo Y, Pan H, Zhang C, Mao G, Huang Y, Li B, Gu T, Wang L, *et al*: Chronic and cumulative adverse life events in women with primary ovarian insufficiency: An exploratory qualitative study. Front Endocrinol (Lausanne) 13: 856044, 2022.
53. Xu YP, Fu JC, Hong ZL, Zeng DF, Guo CQ, Li P and Wu JX: Psychological stressors involved in the pathogenesis of premature ovarian insufficiency and potential intervention measures. Gynecol Endocrinol 40: 2360085, 2024.
54. Schmidt PJ, Luff JA, Haq NA, Vanderhoof VH, Koziol DE, Calis KA, Rubinow DR and Nelson LM: Depression in women with spontaneous 46, XX primary ovarian insufficiency. J Clin Endocrinol Metab 96: E278-E287, 2011.
55. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB and Hollander L: Hormones and menopausal status as predictors of depression in womenin transition to menopause. Arch Gen Psychiatry 61: 62-70, 2004.
56. Bleil ME, Adler NE, Pasch LA, Sternfeld B, Gregorich SE, Rosen MP and Cedars MI: Psychological stress and reproductive aging among pre-menopausal women. Hum Reprod 27: 2720-2728, 2012.
57. Bleil ME, Adler NE, Pasch LA, Sternfeld B, Gregorich SE, Rosen MP and Cedars MI: Depressive symptomatology, psychological stress, and ovarian reserve: A role for psychological factors in ovarian aging? Menopause 19: 1176-1185, 2012.
58. Dong YZ, Zhou FJ and Sun YP: Psychological stress is related to a decrease of serum anti-müllerian hormone level in infertile women. Reprod Biol Endocrinol 15: 51, 2017.

59. Lania A, Gianotti L, Gagliardi I, Bondanelli M, Vena W and Ambrosio MR: Functional hypothalamic and drug-induced amenorrhea: An overview. J Endocrinol Invest 42: 1001-1010, 2019.
60. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, Murad MH, Santoro NF and Warren MP: Functional hypothalamic amenorrhea: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 102: 1413-1439, 2017.
61. Bomba M, Gambera A, Bonini L, Peroni M, Neri F, Scagliola P and Nacinovich R: Endocrine profiles and neuropsychologic correlates of functional hypothalamic amenorrhea in adolescents. Fertil Steril 87: 876-885, 2007.
62. Marcus MD, Loucks TL and Berga SL: Psychological correlates of functional hypothalamic amenorrhea. Fertil Steril 76: 310-316, 2001.
63. Dundon CM, Rellini AH, Tonani S, Santamaria V and Nappi R: Mood disorders and sexual functioning in women with functional hypothalamic amenorrhea. Fertil Steril 94: 2239-2243, 2010.
64. Cai J, Zhang Y, Wang Y, Li S, Wang L, Zheng J, Jiang Y, Dong Y, Zhou H, Hu Y, *et al*: High thyroid stimulating hormone level is associated with hyperandrogenism in euthyroid polycystic ovary syndrome (PCOS) women, independent of age, BMI, and thyroid autoimmunity: A cross-sectional analysis. Front Endocrinol (Lausanne) 10: 222, 2019.
65. Chang AY, Lalia AZ, Jenkins GD, Dutta T, Carter RE, Singh RJ and Nair KS: Combining a nontargeted and targeted metabolomics approach to identify metabolic pathways significantly altered in polycystic ovary syndrome. Metabolism 71: 52-63, 2017.
66. Farrell K and Antoni MH: Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: Biobehavioral mechanisms and interventions. Fertil Steril 94: 1565-1574, 2010.
67. Hillman SC, Bryce C, Caleyachetty R and Dale J: Women's experiences of diagnosis and management of polycystic ovary syndrome: A mixed-methods study in general practice. Br J Gen Pract 70: e322-e329, 2020.
68. Chrousos GP: Stress and disorders of the stress system. Nat Rev Endocrinol 5: 374-381, 2009.
69. Kleinert M, Clemmensen C, Hofmann SM, Moore MC, Renner S, Woods SC, Huypens P, Beckers J, de Angelis MH, Schürmann A, *et al*: Animal models of obesity and diabetes mellitus. Nat Rev Endocrinol 14: 140-162, 2018.
70. Seemann S, Zohles F and Lupp A: Comprehensive comparison of three different animal models for systemic inflammation. J Biomed Sci 24: 60, 2017.
71. Cheon DJ and Orsulic S: Mouse models of cancer. Annu Rev Pathol 6: 95-119, 2011.
72. Antoniuk S, Bijata M, Ponimaskin E and Wlodarczyk J: Chronic unpredictable mild stress for modeling depression in rodents: Meta-analysis of model reliability. Neurosci Biobehav Rev 99: 101-116, 2019.
73. Du Preez A, Onorato D, Eiben I, Musaelyan K, Egeland M, Zunszain PA, Fernandes C, Thuret S and Pariante CM: Chronic stress followed by social isolation promotes depressive-like behaviour, alters microglial and astrocyte biology and reduces hippocampal neurogenesis in male mice. Brain Behav Immun 91: 24-47, 2021.
74. Khan AR, Geiger L, Wiborg O and Czéh B: Stress-induced morphological, cellular and molecular changes in the brain-lessons learned from the chronic mild stress model of depression. Cells 9: 1026, 2020.
75. Xiang Y, Jiang L, Gou J, Sun Y, Zhang D, Xin X, Song Z and Huang J: Chronic unpredictable mild stress-induced mouse ovarian insufficiency by interrupting lipid homeostasis in the ovary. Front Cell Dev Biol 10: 933674, 2022.
76. Fu XY, Chen HH, Zhang N, Ding MX, Qiu YE, Pan XM, Fang YS, Lin YP, Zheng Q and Wang WQ: Effects of chronic unpredictable mild stress on ovarian reserve in female rats: Feasibility analysis of a rat model of premature ovarian failure. Mol Med Rep 18: 532-540, 2018.
77. Ma J, Wang L, Yang D, Luo J, Gao J, Wang J, Guo H, Li J, Wang F, Wu J and Hu R: Chronic stress causes ovarian fibrosis to impair female fertility in mice. Cell Signal 122: 111334, 2024.
78. Ding SM, Shi LG, Xing F, Cui SS, Cheng HR, Liu Y, Ji DM, Liang D, Cao YX and Liu YJ: Melatonin protects against mitochondrial dyshomeostasis and ovarian damage caused by chronic unpredictable mild stress through the eIF2α-AFT4 signaling pathway in mice. Reprod Sci 31: 3191-3201, 2024.
79. Fu X, Zheng Q, Zhang N, Ding M, Pan X, Wang W and Chen H: CUMS promotes the development of premature ovarian insufficiency mediated by nerve growth factor and its receptor in rats. BioMed Res Int 2020: 1946853, 2020.
80. Xu HX, Lin SX, Gong Y, Huo ZX, Zhao CY, Zhu HM and Xi SY: Chaiyu-dixian formula exerts protective effects on ovarian follicular abnormal development in chronic unpredictable mild stress (CUMS) rat model. Front Pharmacol 11: 245, 2020.
81. Zhao X, Ma R, Zhang X, Cheng R, Jiang N, Guo M, Rong B, Liu Y, Chen M, Feng W and Xia T: Reduced growth capacity of preimplantation mouse embryos in chronic unpredictable stress model. Mol Reprod Dev 88: 80-95, 2021.
82. Wu LM, Hu MH, Tong XH, Han H, Shen N, Jin RT, Wang W, Zhou GX, He GP and Liu YS: Chronic unpredictable stress decreases expression of brain-derived neurotrophic factor (BDNF) in mouse ovaries: relationship to oocytes developmental potential. PLoS One 7: e52331, 2012.
83. Li XH, Pang HQ, Qin L, Jin S, Zeng X, Bai Y and Li SW: HSP70 overexpression may play a protective role in the mouse embryos stimulated by CUMS. Reprod Biol Endocrinol 13: 125, 2015.
84. Wu LM, Liu YS, Tong XH, Shen N, Jin RT, Han H, Hu MH, Wang W and Zhou GX: Inhibition of follicular development induced by chronic unpredictable stress is associated with growth and differentiation factor 9 and gonadotropin in mice. Biol Reprod 86: 121, 2012.
85. Sun J, Guo Y, Fan Y, Wang Q, Zhang Q and Lai D: Decreased expression of IDH1 by chronic unpredictable stress suppresses proliferation and accelerates senescence of granulosa cells through ROS activated MAPK signaling pathways. Free Radic Biol Med 169: 122-136, 2021.
86. Du Y, Ma J, Wu T, Li F, Pan J, Du L, Zhang M, Diao X and Wu R: Downgrading breast imaging reporting and data system categories in ultrasound using strain elastography and computer-aided diagnosis system: A multicenter, prospective study. Br J Radiol 97: 1653-1660, 2024.
87. Kala M and Nivsarkar M: Role of cortisol and superoxide dismutase in psychological stress induced anovulation. Gen Comp Endocrinol 225: 117-124, 2016.
88. Gao Y, Chen F, Kong QQ, Ning SF, Yuan HJ, Lian HY, Luo MJ and Tan JH: Stresses on female mice impair oocyte developmental potential: Effects of stress severity and duration on oocytes at the growing follicle stage. Reprod Sci 23: 1148-1157, 2016.
89. Scott K, Phan TT, Boukelmoune N, Heijnen CJ and Dantzer R: Chronic restraint stress impairs voluntary wheel running but has no effect on food-motivated behavior in mice. Brain Behav Immun 107: 319-329, 2023.
90. Chen H, Fu S, Li X, Shi M, Qian J, Zhao S, Yuan P, Ding L, Xia X and Zheng JC: Microglial glutaminase 1 mediates chronic restraint stress-induced depression-like behaviors and synaptic damages. Signal Transduct Target Ther 8: 452, 2023.
91. Chiba S, Numakawa T, Ninomiya M, Richards MC, Wakabayashi C and Kunugi H: Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. Prog Neuropsychopharmacol Biol Psychiatry 39: 112-119, 2012.
92. Buynitsky T and Mostofsky DI: Restraint stress in biobehavioral research: Recent developments. Neurosci Biobehav Rev 33: 1089-1098, 2009.
93. Sun J, Guo Y, Zhang Q, Bu S, Li B, Wang Q and Lai D: Chronic restraint stress disturbs meiotic resumption through APC/C-mediated cyclin B1 excessive degradation in mouse oocytes. Cell Cycle 17: 1591-1601, 2018.
94. Zhang SY, Wang JZ, Li JJ, Wei DL, Sui HS, Zhang ZH, Zhou P and Tan JH: Maternal restraint stress diminishes the developmental potential of oocytes. Biol Reprod 84: 672-681, 2011.
95. Geraghty AC, Muroy SE, Zhao S, Bentley GE, Kriegsfeld LJ and Kaufer D: Knockdown of hypothalamic RFRP3 prevents chronic stress-induced infertility and embryo resorption. Life 4: e04316, 2015.
96. Liang B, Wei DL, Cheng YN, Yuan HJ, Lin J, Cui XZ, Luo MJ and Tan JH: Restraint stress impairs oocyte developmental potential in mice: Role of CRH-induced apoptosis of ovarian cells. Biol Reprod 89: 64, 2013.
97. Li CY, Li ZB, Kong QQ, Han X, Xiao B, Li X, Chang ZL and Tan JH: Restraint-induced corticotrophin-releasing hormone elevation triggers apoptosis of ovarian cells and impairs oocyte competence via activation of the Fas/FasL system. Biol Reprod 99: 828-837, 2018.

98. Huang Y, Liu Q, Huang G, Wen J and Chen G: Hypothalamic kisspeptin neurons regulates energy metabolism and reproduction under chronic stress. Front Endocrinol (Lausanne) 13: 844397, 2022.
99. Sugino N, Nakamura Y, Okuno N, Shimamura K, Teyama T, Ishimatsu M and Kato H: Effects of restraint stress on luteal function in rats during mid-pregnancy. J Reprod Fertil 101: 23-26, 1994.
100. Zhou P, Lian HY, Cui W, Wei DL, Li Q, Liu YX, Liu XY and Tan JH: Maternal-restraint stress increases oocyte aneuploidy by impairing metaphase I spindle assembly and reducing spindle assembly checkpoint proteins in mice. Biol Reprod 86: 83, 2012.
101. Lian HY, Gao Y, Jiao GZ, Sun MJ, Wu XF, Wang TY, Li H and Tan JH: Antioxidant supplementation overcomes the deleterious effects of maternal restraint stress-induced oxidative stress on mouse oocytes. Reproduction 146: 559-568, 2013.
102. Higaki S, Kishi M, Koyama K, Nagano M, Katagiri S, Takada T and Takahashi Y: Early germinal vesicle breakdown is a predictor of high preimplantation developmental competent oocytes in mice. Zygote 25: 41-48, 2017.
103. Zhao XY, Li ZB, Yuan HJ, Han X, Wu JS, Feng XY, Zhang M and Tan JH: Restraint stress and elevation of corticotrophin-releasing hormone in female mice impair oocyte competence through activation of the tumour necrosis factor α (TNF-α) system. Reprod Fertil Dev 32: 862-872, 2020.
104. Guo Y, Sun J, Bu S, Li B, Zhang Q, Wang Q and Lai D: Melatonin protects against chronic stress-induced oxidative meiotic defects in mice MII oocytes by regulating SIRT1. Cell Cycle 19: 1677-1695, 2020.
105. Chen RR, Wang J, Zhang M, Kong QQ, Sun GY, Jin CH and Tan JH: Restraint stress of female mice during oocyte development facilitates oocyte postovulatory aging. Aging (Albany NY) 14: 9186-9199, 2022.
106. Dorfman M, Arancibia S, Fiedler JL and Lara HE: Chronic intermittent cold stress activates ovarian sympathetic nerves and modifies ovarian follicular development in the rat. Biol Reprod 68: 2038-2043, 2003.
107. Bernuci MP, Szawka RE, Helena CVV, Leite CM, Lara HE and Anselmo-Franci JA: Locus coeruleus mediates cold stress-induced polycystic ovary in rats. Endocrinology 149: 2907-2916, 2008.
108. Barra R, Cruz G, Mayerhofer A, Paredes A and Lara HE: Maternal sympathetic stress impairs follicular development and puberty of the offspring. Reproduction 148: 137-145, 2014.
109. Bernuci MP, Leite CM, Barros P, Kalil B, Leoni GB, Del Bianco-Borges B, Franci CR, Szawka RE, Lara HE and Anselmo-Franci JA: Transitory activation of the central and ovarian norepinephrine systems during cold stress-induced polycystic ovary in rats. J Neuroendocrinol 25: 23-33, 2013.
110. Pacak K, Palkovits M, Yadid G, Kvetnansky R, Kopin IJ and Goldstein DS: Heterogeneous neurochemical responses to different stressors: A test of Selye's doctrine of nonspecificity. Am J Physiol 275: R1247-R1255, 1998.
111. Riquelme R, Ruz F, Mayerhofer A and Lara HE: Role of ovarian sympathetic nerves and cholinergic local system during cold stress. J Endocrinol 242: 115-124, 2019.
112. Casillas F, Betancourt M, Juárez-Rojas L, Ducolomb Y, López A, Ávila-Quintero A, Zamora J, Ommati MM and Retana-Márquez S: Chronic stress detrimentally affects in vivo maturation in rat oocytes and oocyte viability at all phases of the estrous cycle. Animals (Basel) 11: 2478, 2021.
113. Wang D, Cheng X, Fang H, Ren Y, Li X, Ren W, Xue B and Yang C: Effect of cold stress on ovarian & uterine microcirculation in rats and the role of endothelin system. Reprod Biol Endocrinol 18: 29, 2020.
114. Retana-Márquez S, Juárez-Rojas L, Ávila-Quintero A, Rojas-Maya S, Perera G, Casillas F, Betancourt M and Gómez-Quiroz L: Neuroendocrine disruption is associated to infertility in chronically stressed female rats. Reprod Biol 20: 474-483, 2020.
115. Keremu A, Yaoliwasi A, Tuerhong M, Kadeer N, Heyi, Yiming A and Yilike X: Research on the establishment of chronic stress-induced premature ovarian failure the rat model and effects of Chinese medicine Muniziqi treatment. Mol Reprod Dev 86: 175-186, 2019.
116. Ernsberger U, Deller T and Rohrer H: The sympathies of the body: Functional organization and neuronal differentiation in the peripheral sympathetic nervous system. Cell Tissue Res 386: 455-475, 2021.
117. Espinoza JA, Navarrete MI, Linares R, Chaparro-Ortega A, Ramírez DA, Rosas G, Vieyra E, Domínguez R and Morales-Ledesma L: Effects of chronic exposure to cold stress on ovarian functions in prepubertal rats. Reprod Biol 23: 100756, 2023.
118. Divyashree S and Yajurvedi HN: Long-term chronic stress exposure induces PCO phenotype in rat. Reproduction 152: 765-774, 2016.
119. Bunsueb S, Lapyuneyong N, Tongpan S, Arun S and Iamsaard S: Chronic stress increases the tyrosine phosphorylation in female reproductive organs: An experimental study. Int J Reprod Biomed 19: 87-96, 2021.
120. Kim J and You S: High housing density-induced chronic stress diminishes ovarian reserve via granulosa cell apoptosis by angiotensin II overexpression in mice. Int J Mol Sci 23: 8614, 2022.
121. Xi W, Mao H, Cui Z, Yao H, Shi R and Gao Y: Scream sound-induced chronic psychological stress results in diminished ovarian reserve in adult female rat. Endocrinology 163: bqac042, 2022.
122. Ghatebi M, Zavareh S, Lashkarbolouki T and Elahdadi Salmani M: Implications from early life stress on the development of mouse ovarian follicles: Focus on oxidative stress. J Obstet Gynaecol Res 45: 1506-1514, 2019.
123. Yuan J, Yu Y, Liu D and Sun Y: Associations between distinct dimensions of early life adversity and accelerated reproductive strategy among middle-aged women in China. Am J Obstet Gynecol 226: 104.e1-104.e14, 2022.
124. Mishra GD, Cooper R, Tom SE and Kuh D: Early life circumstances and their impact on menarche and menopause. Womens Health (Lond) 5: 175-190, 2009.
125. Wang N, Huang Y, Wen J, Su Q, Huang Y, Cai L, Lin W, Zong L, Huang H, Qian X, *et al*: Early life exposure to famine and reproductive aging among Chinese women. Menopause 26: 463-468, 2019.
126. Liu YX, Cheng YN, Miao YL, Wei DL, Zhao LH, Luo MJ and Tan JH: Psychological stress on female mice diminishes the developmental potential of oocytes: A study using the predatory stress model. PLoS One 7: e48083, 2012.
127. Onalan E, Erbay B, Buran İK, Erol D, Tektemur A, Kuloglu T and Ozercan IH: Effects and mechanism of AP39 on ovarian functions in rats exposed to cisplatin and chronic immobilization stress. J Menopausal Med 30: 104-119, 2024.
128. Yuan HJ, Li ZB, Zhao XY, Sun GY, Wang GL, Zhao YQ, Zhang M and Tan JH: Glucocorticoids impair oocyte competence and trigger apoptosis of ovarian cells via activating the TNF-α system. Reproduction 160: 129-140, 2020.
129. Becker M, Pinhasov A and Ornoy A: Animal models of depression: What can they teach Us about the human disease? Diagnostics (Basel) 11: 123, 2021.
130. Kendler KS: The genealogy of major depression: Symptoms and signs of melancholia from 1880 to 1900. Mol Psychiatry 22: 1539-1553, 2017.
131. Liu MY, Yin CY, Zhu LJ, Zhu XH, Xu C, Luo CX, Chen H, Zhu DY and Zhou QG: Sucrose preference test for measurement of stress-induced anhedonia in mice. Nat Protoc 13: 1686-1698, 2018.
132. Primo MJ, Fonseca-Rodrigues D, Almeida A, Teixeira PM and Pinto-Ribeiro F: Sucrose preference test: A systematic review of protocols for the assessment of anhedonia in rodents. Eur Neuropsychopharmacol 77: 80-92, 2023.
133. Verharen JPH, de Jong JW, Zhu Y and Lammel S: A computational analysis of mouse behavior in the sucrose preference test. Nat Commun 14: 2419, 2023.
134. Porsolt RD, Le Pichon M and Jalfre M: Depression: A new animal model sensitive to antidepressant treatments. Nature 266: 730-732, 1977.
135. Cryan JF, Mombereau C and Vassout A: The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 29: 571-625, 2005.
136. Prut L and Belzung C: The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: A review. Eur J Pharmacol 463: 3-33, 2003.
137. Kraeuter AK, Guest PC and Sarnyai Z: The open field test for measuring locomotor activity and anxiety-like behavior. Methods Mol Biol 1916: 99-103, 2019.
138. Seibenhener ML and Wooten MC: Use of the open field maze to measure locomotor and anxiety-like behavior in mice. J Vis Exp: e52434, 2015.

139. Bourin M and Hascoët M: The mouse light/dark box test. Eur J Pharmacol 463: 55-65, 2003.
140. Walf AA and Frye CA: The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc 2: 322-328, 2007.
141. Kraeuter AK, Guest PC and Sarnyai Z: The elevated plus maze test for measuring anxiety-like behavior in rodents. Methods Mol Biol 1916: 69-74, 2019.
142. Schrader AJ, Taylor RM, Lowery-Gionta EG and Moore NLT: Repeated elevated plus maze trials as a measure for tracking within-subjects behavioral performance in rats (Rattus norvegicus). PLoS One 13: e0207804, 2018.
143. Pietropaolo S: Mood and anxiety-related phenotypes in mice: Characterization using behavioral tests-Edited by T. D. Gould. Genes Brain Behav 9: 544-544, 2010.
144. Bae J, Lynch CD, Kim S, Sundaram R, Sapra KJ and Buck Louis GM: Preconception stress and the secondary sex ratio in a population-based preconception cohort. Fertil Steril 107: 714-722, 2017.
145. Ulrich-Lai YM and Herman JP: Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10: 397-409, 2009.
146. Jacobson L: Hypothalamic-pituitary-adrenocortical axis regulation. Endocrinol Metab Clin North Am 34: 271-292, vii, 2005.
147. McCall JG, Al-Hasani R, Siuda ER, Hong DY, Norris AJ, Ford CP and Bruchas MR: CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. Neuron 87: 605-620, 2015.
148. Agorastos A and Chrousos GP: The neuroendocrinology of stress: The stress-related continuum of chronic disease development. Mol Psychiatry 27: 502-513, 2022.
149. Yoo ES, Yu J and Sohn JW: Neuroendocrine control of appetite and metabolism. Exp Mol Med 53: 505-516, 2021.
150. Di Comite G, Grazia Sabbadini M, Corti A, Rovere-Querini P and Manfredi AA: Conversation galante: How the immune and the neuroendocrine systems talk to each other. Autoimmun Rev 7: 23-29, 2007.
151. Smeenk JMJ, Verhaak CM, Vingerhoets AJJM, Sweep CGJ, Merkus JMWM, Willemsen SJ, van Minnen A, Straatman H and Braat DD: Stress and outcome success in IVF: The role of self-reports and endocrine variables. Hum Reprod 20: 991-996, 2005.
152. Hjollund NHI, Jensen TK, Bonde JP, Henriksen TB, Andersson AM, Kolstad HA, Ernst E, Giwercman A, Skakkebaek NE and Olsen J: Distress and reduced fertility: A follow-up study of first-pregnancy planners. Fertil Steril 72: 47-53, 1999.
153. Ates S, Yesil G, Sevket O, Molla T and Yildiz S: Comparison of metabolic profile and abdominal fat distribution between karyotypically normal women with premature ovarian insufficiency and age matched controls. Maturitas 79: 306-310, 2014.
154. Huang Y, Lv Y, Qi T, Luo Z, Meng X, Ying Q, Li D, Li C, Lan Y, Chu K, *et al*: Metabolic profile of women with premature ovarian insufficiency compared with that of age-matched healthy controls. Maturitas 148: 33-39, 2021.
155. Ferin M: Clinical review 105: Stress and the reproductive cycle. J Clin Endocrinol Metab 84: 1768-1774, 1999.
156. Chrousos GP, Torpy DJ and Gold PW: Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: Clinical implications. Ann Intern Med 129: 229-240, 1998.
157. Harlow CR, Fahy UM, Talbot WM, Wardle PG and Hull MG: Stress and stress-related hormones during in-vitro fertilization treatment. Hum Reprod 11: 274-279, 1996.
158. Demyttenaere K, Nijs P, Evers-Kiebooms G and Koninckx PR: Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. Psychoneuroendocrinology 17: 655-665, 1992.
159. Pal L, Bevilacqua K and Santoro NF: Chronic psychosocial stressors are detrimental to ovarian reserve: A study of infertile women. J Psychosom Obstet Gynecol 31: 130-139, 2010.
160. Andersen CY: Effect of glucocorticoids on spontaneous and follicle-stimulating hormone induced oocyte maturation in mouse oocytes during culture. J Steroid Biochem Mol Biol 85: 423-427, 2003.
161. Yuan HJ, Han X, He N, Wang GL, Gong S, Lin J, Gao M and Tan JH: Glucocorticoids impair oocyte developmental potential by triggering apoptosis of ovarian cells via activating the Fas system. Sci Rep 6: 24036, 2016.
162. Kalantaridou SN, Zoumakis E, Makrigiannakis A, Lavasidis LG, Vrekoussis T and Chrousos GP: Corticotropin-releasing hormone, stress and human reproduction: An update. J Reprod Immunol 85: 33-39, 2010.
163. Rivier C and Vale W: Influence of corticotropin-releasing factor on reproductive functions in the rat. Endocrinology 114: 914-921, 1984.
164. Breen KM, Thackray VG, Hsu T, Mak-McCully RA, Coss D and Mellon PL: Stress levels of glucocorticoids inhibit LHβ-subunit gene expression in gonadotrope cells. Mol Endocrinol 26: 1716-1731, 2012.
165. Luo E, Stephens SBZ, Chaing S, Munaganuru N, Kauffman AS and Breen KM: Corticosterone blocks ovarian cyclicity and the LH surge via decreased kisspeptin neuron activation in female mice. Endocrinology 157: 1187-1199, 2016.
166. Roozendaal MM, Swarts JJM, Van Maanen JC, Wiegant VM and Mattheij JA: Inhibition of the LH surge in cyclic rats by stress is not mediated by opioids. Life Sci 60: 735-742, 1997.
167. Horowitz MA and Zunszain PA: Neuroimmune and neuroendocrine abnormalities in depression: Two sides of the same coin. Ann N Y Acad Sci 1351: 68-79, 2015.
168. Berga SL, Daniels TL and Giles DE: Women with functional hypothalamic amenorrhea but not other forms of anovulation display amplified cortisol concentrations. Fertil Steril 67: 1024-1030, 1997.
169. Deady LD and Sun J: A follicle rupture assay reveals an essential role for follicular adrenergic signaling in drosophila ovulation. PLoS Genet 11: e1005604, 2015.
170. Aguado LI: Role of the central and peripheral nervous system in the ovarian function. Microsc Res Tech 59: 462-473, 2002.
171. Lara HE, Dorfman M, Venegas M, Luza SM, Luna SL, Mayerhofer A, Guimaraes MA, Rosa E Silva AA and Ramírez VD: Changes in sympathetic nerve activity of the mammalian ovary during a normal estrous cycle and in polycystic ovary syndrome: Studies on norepinephrine release. Microsc Res Tech 59: 495-502, 2002.
172. Morales-Ledesma L, Linares R, Rosas G, Morán C, Chavira R, Cárdenas M and Domínguez R: Unilateral sectioning of the superior ovarian nerve of rats with polycystic ovarian syndrome restores ovulation in the innervated ovary. Reprod Biol Endocrinol 8: 99, 2010.
173. Dissen GA, Romero C, Paredes A and Ojeda SR: Neurotrophic control of ovarian development. Microsc Res Tech 59: 509-515, 2002.
174. Uchida S and Kagitani F: Autonomic nervous regulation of ovarian function by noxious somatic afferent stimulation. J Physiol Sci 65: 1-9, 2015.
175. Acuña E, Fornes R, Fernandois D, Garrido MP, Greiner M, Lara HE and Paredes AH: Increases in norepinephrine release and ovarian cyst formation during ageing in the rat. Reprod Biol Endocrinol 7: 64, 2009.
176. Casillas F, Flores-González A, Juárez-Rojas L, López A, Betancourt M, Casas E, Bahena I, Bonilla E and Retana-Márquez S: Chronic stress decreases fertility parameters in female rats. Syst Biol Reprod Med 69: 234-244, 2023.
177. Fernandois D, Cruz G, Na EK, Lara HE and Paredes AH: Kisspeptin level in the aging ovary is regulated by the sympathetic nervous system. J Endocrinol 232: 97-105, 2017.
178. Saller S, Merz-Lange J, Raffael S, Hecht S, Pavlik R, Thaler C, Berg D, Berg U, Kunz L and Mayerhofer A: Norepinephrine, active norepinephrine transporter, and norepinephrine-metabolism are involved in the generation of reactive oxygen species in human ovarian granulosa cells. Endocrinology 153: 1472-1483, 2012.
179. Zhang L, Gao J and Cui S: miR-21 is involved in norepinephrine-mediated rat granulosa cell apoptosis by targeting SMAD7. J Mol Endocrinol 58: 199-210, 2017.
180. Li XH, Ma YG, Geng LH, Qin L, Hu H and Li SW: Baseline psychological stress and ovarian norepinephrine levels negatively affect the outcome of in vitro fertilisation. Gynecol Endocrinol 27: 139-143, 2011.
181. Lynch CD, Sundaram R, Maisog JM, Sweeney AM and Louis GMB: Preconception stress increases the risk of infertility: Results from a couple-based prospective cohort study-the LIFE study. Hum Reprod 29: 1067-1075, 2014.
182. Hackett RA and Steptoe A: Type 2 diabetes mellitus and psychological stress-a modifiable risk factor. Nat Rev Endocrinol 13: 547-560, 2017.

183. Afrisham R, Paknejad M, Soliemanifar O, Sadegh-Nejadi S, Meshkani R and Ashtary-Larky D: The influence of psychological stress on the initiation and progression of diabetes and cancer. Int J Endocrinol Metab 17: e67400, 2019.
184. Joseph JJ and Golden SH: Cortisol dysregulation: The bidirectional link between stress, depression, and type 2 diabetes mellitus. Ann N Y Acad Sci 1391: 20-34, 2017.
185. Balkan F, Cetin N, Usluogullari CA, Unal OK and Usluogullari B: Evaluation of the ovarian reserve function in patients with metabolic syndrome in relation to healthy controls and different age groups. J Ovarian Res 7: 63, 2014.
186. Isik S, Ozcan HN, Ozuguz U, Tutuncu YA, Berker D, Alimli AG, Akbaba G, Karademir MA and Guler S: Evaluation of ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with type 2 diabetes mellitus. J Clin Endocrinol Metab 97: 261-269, 2012.
187. Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM and Clouse RE: Depression and poor glycemic control: A meta-analytic review of the literature. Diabetes Care 23: 934-942, 2000.
188. Yaribeygi H, Sathyapalan T, Atkin SL and Sahebkar A: Molecular mechanisms linking oxidative stress and diabetes mellitus. Oxid Med Cell Longev 2020: 8609213, 2020.
189. Grigsby AB, Anderson RJ, Freedland KE, Clouse RE and Lustman PJ: Prevalence of anxiety in adults with diabetes: A systematic review. J Psychosom Res 53: 1053-1060, 2002.
190. Razzoli M, Pearson C, Crow S and Bartolomucci A: Stress, overeating, and obesity: Insights from human studies and preclinical models. Neurosci Biobehav Rev 76: 154-162, 2017.
191. Codner E, Merino PM and Tena-Sempere M: Female reproduction and type 1 diabetes: From mechanisms to clinical findings. Hum Reprod Update 18: 568-585, 2012.
192. Nandi A and Poretsky L: Diabetes and the female reproductive system. Endocrinol Metab Clin North Am 42: 915-946, 2013.
193. Dri M, Klinger FG and De Felici M: The ovarian reserve as target of insulin/IGF and ROS in metabolic disorder-dependent ovarian dysfunctions. Reprod Fertil 2: R103-R112, 2021.
194. Barbieri RL, Makris A and Ryan KJ: Effects of insulin on steroidogenesis in cultured porcine ovarian theca. Fertil Steril 40: 237-241, 1983.
195. Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW and Ryan KJ: Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. J Clin Endocrinol Metab 62: 904-910, 1986.
196. Cara JF and Rosenfield RL: Insulin-like growth factor I and insulin potentiate luteinizing hormone-induced androgen synthesis by rat ovarian thecal-interstitial cells. Endocrinology 123: 733-739, 1988.
197. Hudish LI, Reusch JE and Sussel L: β Cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J Clin Invest 129: 4001-4008, 2019.
198. Escobar-Morreale HF, Roldán B, Barrio R, Alonso M, Sancho J, De La Calle H and García-Robles R: High prevalence of the polycystic ovary syndrome and hirsutism in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 85: 4182-4187, 2000.
199. Diamanti-Kandarakis E, Piperi C, Patsouris E, Korkolopoulou P, Panidis D, Pawelczyk L, Papavassiliou AG and Duleba AJ: Immunohistochemical localization of advanced glycation end-products (AGEs) and their receptor (RAGE) in polycystic and normal ovaries. Histochem Cell Biol 127: 581-589, 2007.
200. Secomandi L, Borghesan M, Velarde M and Demaria M: The role of cellular senescence in female reproductive aging and the potential for senotherapeutic interventions. Hum Reprod Update 28: 172-189, 2022.
201. Willis DS, Watson H, Mason HD, Galea R, Brincat M and Franks S: Premature response to luteinizing hormone of granulosa cells from anovulatory women with polycystic ovary syndrome: Relevance to mechanism of anovulation. J Clin Endocrinol Metab 83: 3984-3991, 1998.
202. Lee J, Lee HC, Kim SY, Cho GJ and Woodruff TK: Poorly-controlled type 1 diabetes mellitus impairs LH-LHCGR signaling in the ovaries and decreases female fertility in mice. Yonsei Med J 60: 667-678, 2019.
203. Zargar AH, Gupta VK, Wani AI, Masoodi SR, Bashir MI, Laway BA, Ganie MA and Salahuddin M: Prevalence of ultrasonography proved polycystic ovaries in North Indian women with type 2 diabetes mellitus. Reprod Biol Endocrinol 3: 35, 2005.
204. Peppard HR, Marfori J, Iuorno MJ and Nestler JE: Prevalence of polycystic ovary syndrome among premenopausal women with type 2 diabetes. Diabetes Care 24: 1050-1052, 2001.
205. Khalil N, Sutton-Tyrrell K, Strotmeyer ES, Greendale GA, Vuga M, Selzer F, Crandall CJ and Cauley JA: Menopausal bone changes and incident fractures in diabetic women: A cohort study. Osteoporos Int 22: 1367-1376, 2011.
206. Sekhar TVDS, Medarametla S, Rahman A and Adapa SS: Early menopause in type 2 diabetes-A study from a South Indian tertiary care centre. J Clin Diagn Res 9: OC08-OC10, 2015.
207. Qin X, Du J, He R, Li Y, Zhu Q, Li Y, Li H and Liang X: Adverse effects of type 2 diabetes mellitus on ovarian reserve and pregnancy outcomes during the assisted reproductive technology process. Front Endocrinol (Lausanne) 14: 1274327, 2023.
208. Carr MC: The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 88: 2404-2411, 2003.
209. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA and Barrett-Connor E; Heart and Estrogen/progestin Replacement Study: Glycemic effects of postmenopausal hormone therapy: The heart and estrogen/progestin replacement study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 138: 1-9, 2003.
210. Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, Bassford T, Burke G, Torrens J and Howard BV; Women's Health Initiative Investigators: Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the women's health initiative hormone trial. Diabetologia 47: 1175-1187, 2004.
211. Wagner JD, Thomas MJ, Williams JK, Zhang L, Greaves KA and Cefalu WT: Insulin sensitivity and cardiovascular risk factors in ovariectomized monkeys with estradiol alone or combined with nomegestrol acetate. J Clin Endocrinol Metab 83: 896-901, 1998.
212. Kumagai S, Holmäng A and Björntorp P: The effects of oestrogen and progesterone on insulin sensitivity in female rats. Acta Physiol Scand 149: 91-97, 1993.
213. Cantave CY, Ruttle PL, Coté SM, Lupien SJ, Geoffroy MC, Vitaro F, Brendgen M, Tremblay R, Boivin M and Ouellet-Morin I: Body mass index across development and adolescent hair cortisol: The role of persistence, variability, and timing of exposure. Int J Obes (Lond): Oct 4, 2024 (Epub ahead of print).
214. Christakoudi S, Asimakopoulos AG, Riboli E and Tsilidis KK: Links between the genetic determinants of morning plasma cortisol and body shape: A two-sample Mendelian randomisation study. Sci Rep 14: 3230, 2024.
215. Kühnel A, Hagenberg J, Knauer-Arloth J, Ködel M, Czisch M, Sämann PG, BeCOME working group; Binder EB and Kroemer NB: Stress-induced brain responses are associated with BMI in women. Commun Biol 6: 1031, 2023.
216. Lin YC, Lin CY, Saffari M, Tsai MC, Chang YH, Strong C, Chen JK, Hsieh YP, Yang YN and Latner JD: Weight stigma is associated with body mass index among college students in Taiwan: The mediated role of internalized weight stigma. BMC Psychol 11: 365, 2023.
217. Fardet L and Fève B: Systemic glucocorticoid therapy: A review of its metabolic and cardiovascular adverse events. Drugs 74: 1731-1745, 2014.
218. Santosa A, Rosengren A, Ramasundarahettige C, Rangarajan S, Gulec S, Chifamba J, Lear SA, Poirier P, Yeates KE, Yusuf R, *et al*: Psychosocial risk factors and cardiovascular disease and death in a population-based cohort from 21 low-, middle-, and high-income countries. JAMA Netw Open 4: e2138920, 2021.
219. Ponti F, Santoro A, Mercatelli D, Gasperini C, Conte M, Martucci M, Sangiorgi L, Franceschi C and Bazzocchi A: Aging and imaging assessment of body composition: From fat to facts. Front Endocrinol (Lausanne) 10: 861, 2020.
220. Van Der Valk ES, Savas M and Van Rossum EFC: Stress and obesity: Are there more susceptible individuals? Curr Obes Rep 7: 193-203, 2018.
221. Chen X, Xiao Z, Cai Y, Huang L and Chen C: Hypothalamic mechanisms of obesity-associated disturbance of hypothalamic-pituitary-ovarian axis. Trends Endocrinol Metab 33: 206-217, 2022.
222. Morimoto A, Rose RD, Smith KM, Dinh DT, Umehara T, Winstanley YE, Shibahara H, Russell DL and Robker RL: Granulosa cell metabolism at ovulation correlates with oocyte competence and is disrupted by obesity and aging. Hum Reprod 39: 2053-2066, 2024.
223. Schon SB, Cabre HE and Redman LM: The impact of obesity on reproductive health and metabolism in reproductive-age females. Fertil Steril 122: 194-203, 2024.

224. Martinuzzi K, Ryan S, Luna M and Copperman AB: Elevated body mass index (BMI) does not adversely affect in vitro fertilization outcome in young women. J Assist Reprod Genet 25: 169-175, 2008.
225. Bernardi LA, Carnethon MR, de Chavez PJ, Ikhena DE, Neff LM, Baird DD and Marsh EE: Relationship between obesity and anti-Müllerian hormone in reproductive-aged African American women. Obesity (Silver Spring) 25: 229-235, 2017.
226. Moy V, Jindal S, Lieman H and Buyuk E: Obesity adversely affects serum anti-müllerian hormone (AMH) levels in Caucasian women. J Assist Reprod Genet 32: 1305-1311, 2015.
227. Freeman EW, Gracia CR, Sammel MD, Lin H, Lim LCL and Strauss JF III: Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril 87: 101-106, 2007.
228. Wang Y, Wu L, Yang Z, Xu R, Duan Y, Lin J, Cui X, Fan C, Zhou Y, Bao W, *et al*: Association of body mass index with serum anti-Müllerian hormone and inhibin B levels among 8323 women attending a reproductive medical center: A cross-sectional study. Endocrine 75: 284-292, 2022.
229. Douchi T, Kuwahata R, Yamamoto S, Oki T, Yamasaki H and Nagata Y: Relationship of upper body obesity to menstrual disorders. Acta Obstet Gynecol Scand 81: 147-150, 2002.
230. Rittmaster RS, Deshwal N and Lehman L: The role of adrenal hyperandrogenism, insulin resistance, and obesity in the pathogenesis of polycystic ovarian syndrome. J Clin Endocrinol Metab 76: 1295-1300, 1993.
231. Di Berardino C, Peserico A, Capacchietti G, Zappacosta A, Bernabò N, Russo V, Mauro A, El Khatib M, Gonnella F, Konstantinidou F, *et al*: High-fat diet and female fertility across lifespan: A comparative lesson from mammal models. Nutrients 14: 4341, 2022.
232. Wang N, Luo LL, Xu JJ, Xu MY, Zhang XM, Zhou XL, Liu WJ and Fu YC: Obesity accelerates ovarian follicle development and follicle loss in rats. Metabolism 63: 94-103, 2014.
233. Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE and Moley KH: Diet-induced obesity model: Abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology 151: 4039-4046, 2010.
234. Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, Schedl T and Moley KH: High fat diet induced developmental defects in the mouse: Oocyte meiotic aneuploidy and fetal growth retardation/brain defects. PLoS One 7: e49217, 2012.
235. Reynolds KA, Boudoures AL, Chi MMY, Wang Q and Moley KH: Adverse effects of obesity and/or high-fat diet on oocyte quality and metabolism are not reversible with resumption of regular diet in mice. Reprod Fertil Dev 27: 716-724, 2015.
236. Machtinger R, Combelles CMH, Missmer SA, Correia KF, Fox JH and Racowsky C: The association between severe obesity and characteristics of failed fertilized oocytes. Hum Reprod 27: 3198-3207, 2012.
237. Kloos J, Perez J and Weinerman R: Increased body mass index is negatively associated with ovarian reserve as measured by anti-Müllerian hormone in patients with polycystic ovarian syndrome. Clin Obes 29: e12638, 2024.
238. Beroukhim G, Esencan E and Seifer DB: Impact of sleep patterns upon female neuroendocrinology and reproductive outcomes: A comprehensive review. Reprod Biol Endocrinol 20: 16, 2022.
239. Yan J, Zhang X, Zhu K, Yu M, Liu Q, De Felici M, Zhang T, Wang J and Shen W: Sleep deprivation causes gut dysbiosis impacting on systemic metabolomics leading to premature ovarian insufficiency in adolescent mice. Theranostics 14: 3760-3776, 2024.
240. Weng L, Hong H, Zhang Q, Xiao C, Zhang Q, Wang Q, Huang J and Lai D: Sleep deprivation triggers the excessive activation of ovarian primordial follicles via β2 adrenergic receptor signaling. Adv Sci (Weinh) 11: e2402393, 2024.
241. Andersen ML, Alvarenga TAF, Guindalini C, Perry JC, Silva A, Zager A and Tufik S: Paradoxical sleep deprivation influences sexual behavior in female rats. J Sex Med 6: 2162-2172, 2009.
242. Koehl M, Battle S and Meerlo P: Sex differences in sleep: The response to sleep deprivation and restraint stress in mice. Sleep 29: 1224-1231, 2006.
243. Yang CK, Tsai HD, Wu CH and Cho CL: The role of glucocorticoids in ovarian development of sleep deprived rats. Taiwan J Obstet Gynecol 58: 122-127, 2019.
244. Yang CK, Wu RSC, Wu CH, Lin TRY and Tsai HD: Sleep deprivation enhances peripheral serotonin secretion to regulate the large follicle steroidogenesis of rats. Taiwan J Obstet Gynecol 54: 260-265, 2015.
245. Stock D, Knight JA, Raboud J, Cotterchio M, Strohmaier S, Willett W, Eliassen AH, Rosner B, Hankinson SE and Schernhammer E: Rotating night shift work and menopausal age. Hum Reprod 34: 539-548, 2019.
246. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M and Qin L: Melatonin as an antioxidant: Under promises but over delivers. J Pineal Res 61: 253-278, 2016.
247. Tamura H, Takasaki A, Taketani T, Tanabe M, Kizuka F, Lee L, Tamura I, Maekawa R, Asada H, Yamagata Y and Sugino N: Melatonin as a free radical scavenger in the ovarian follicle. Endocr J 60: 1-13, 2013.
248. Lahiri DK, Ge Y, Sharman EH and Bondy SC: Age-related changes in serum melatonin in mice: Higher levels of combined melatonin and 6-hydroxymelatonin sulfate in the cerebral cortex than serum, heart, liver and kidney tissues. J Pineal Res 36: 217-223, 2004.
249. Tanabe M, Tamura H, Taketani T, Okada M, Lee L, Tamura I, Maekawa R, Asada H, Yamagata Y and Sugino N: Melatonin protects the integrity of granulosa cells by reducing oxidative stress in nuclei, mitochondria, and plasma membranes in mice. J Reprod Dev 61: 35-41, 2015.
250. Shen M, Cao Y, Jiang Y, Wei Y and Liu H: Melatonin protects mouse granulosa cells against oxidative damage by inhibiting FOXO1-mediated autophagy: Implication of an antioxidation-independent mechanism. Redox Biol 18: 138-157, 2018.
251. Zhai B, Li X, Zhao Z, Cao Y, Liu X, Liu Z, Ma H and Lu W: Melatonin protects the apoptosis of sheep granulosa cells by suppressing oxidative stress via MAP3K8 and FOS pathway. Genes (Basel) 14: 1067, 2023.
252. Xu G, Dong Y, Wang Z, Ding H, Wang J, Zhao J, Liu H and Lv W: Melatonin attenuates oxidative stress-induced apoptosis of bovine ovarian granulosa cells by promoting mitophagy via SIRT1/FoxO1 signaling pathway. Int J Mol Sci 24: 12854, 2023.
253. Tamura H, Takasaki A, Miwa I, Taniguchi K, Maekawa R, Asada H, Taketani T, Matsuoka A, Yamagata Y, Shimamura K, *et al*: Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. J Pineal Res 44: 280-287, 2008.
254. Zhang H, Li C, Wen D, Li R, Lu S, Xu R, Tang Y, Sun Y, Zhao X, Pan M and Ma B: Melatonin improves the quality of maternally aged oocytes by maintaining intercellular communication and antioxidant metabolite supply. Redox Biol 49: 102215, 2022.
255. Lord T, Nixon B, Jones KT and Aitken RJ: Melatonin prevents postovulatory oocyte aging in the mouse and extends the window for optimal fertilization in vitro. Biol Reprod 88: 67, 2013.
256. Zhang M, Lu Y, Chen Y, Zhang Y and Xiong B: Insufficiency of melatonin in follicular fluid is a reversible cause for advanced maternal age-related aneuploidy in oocytes. Redox Biol 28: 101327, 2020.
257. Yang D, Mu Y, Wang J, Zou W, Zou H, Yang H, Zhang C, Fan Y, Zhang H, Zhang H, *et al*: Melatonin enhances the developmental potential of immature oocytes from older reproductive-aged women by improving mitochondrial function. Heliyon 9: e19366, 2023.
258. Li C, He X, Huang Z, Han L, Wu X, Li L, Xin Y, Ge J, Sha J, Yin Z and Wang Q: Melatonin ameliorates the advanced maternal age-associated meiotic defects in oocytes through the SIRT2-dependent H4K16 deacetylation pathway. Aging (Albany NY) 12: 1610-1623, 2020.
259. Takasaki A, Nakamura Y, Tamura H, Shimamura K and Morioka H: Melatonin as a new drug for improving oocyte quality. Reprod Med Biol 2: 139-144, 2004.
260. Baden MY, Hu FB, Vetter C, Schernhammer E, Redline S and Huang T: Sleep duration patterns in early to middle adulthood and subsequent risk of type 2 diabetes in women. Diabetes Care 43: 1219-1226, 2020.
261. Rooney KL and Domar AD: The impact of stress on fertility treatment. Curr Opin Obstet Gynecol 28: 198-201, 2016.
262. Ramezanzadeh F, Noorbala AA, Abedinia N, Rahimi Forooshani A and Naghizadeh MM: Psychiatric intervention improved pregnancy rates in infertile couples. Malays J Med Sci 18: 16-24, 2011.
263. Rock J, Tietze C and McLaughlin HB: Effect of adoption on infertility. Fertil Steril 16: 305-312, 1965.
264. Weir WC and Weir DR: Adoption and subsequent conceptions. Fertil Steril 17: 283-288, 1966.
265. Nakao M, Shirotsuki K and Sugaya N: Cognitive-behavioral therapy for management of mental health and stress-related disorders: Recent advances in techniques and technologies. Biopsychosoc Med 15: 16, 2021.

266. Hoffman SG and Smits JAJ: Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry 69: 621-632, 2008.
267. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ and Foa EB: A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin Psychol Rev 30: 635-641, 2010.
268. Olatunji BO, Davis ML, Powers MB and Smits JAJ: Cognitive-behavioral therapy for obsessive-compulsive disorder: A meta-analysis of treatment outcome and moderators. J Psychiatr Res 47: 33-41, 2013.
269. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A and Dobson KS: A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry 58: 376-385, 2013.
270. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT and Fang A: The efficacy of cognitive behavioral therapy: A review of meta-analyses. Cogn Ther Res 36: 427-440, 2012.
271. Golshani F, Hasanpour S, Mirghafourvand M and Esmaeilpour K: Effect of cognitive behavioral therapy-based counseling on perceived stress in pregnant women with history of primary infertility: A controlled randomized clinical trial. BMC Psychiatry 21: 278, 2021.
272. Domar AD, Rooney KL, Wiegand B, Orav EJ, Alper MM, Berger BM and Nikolovski J: Impact of a group mind/body intervention on pregnancy rates in IVF patients. Fertil Steril 95: 2269-2273, 2011.
273. Faramarzi M, Pasha H, Esmailzadeh S, Kheirkhah F, Heidary S and Afshar Z: The effect of the cognitive behavioral therapy and pharmacotherapy on infertility stress: A randomized controlled trial. Int J Fertil Steril 7: 199-206, 2013.
274. Sexton MB, Byrd MR, O'Donohue WT and Jacobs NN: Web-based treatment for infertility-related psychological distress. Arch Womens Ment Health 13: 347-358, 2010.
275. John JB, Chellaiyan DVG, Gupta S and Nithyanandham R: How effective the mindfulness-based cognitive behavioral therapy on quality of life in women with menopause. J Midlife Health 13: 169-174, 2022.
276. Green SM and Furtado M: Cognitive behavioral therapy for sexual concerns during perimenopause: A four session study protocol. Front Glob Womens Health 2: 744748, 2021.
277. Green SM, Donegan E, Frey BN, Fedorkow DM, Key BL, Streiner DL and McCabe RE: Cognitive behavior therapy for menopausal symptoms (CBT-Meno): A randomized controlled trial. Menopause 26: 972-980, 2019.
278. Green SM, Haber E, McCabe RE and Soares CN: Cognitive-behavioral group treatment for menopausal symptoms: A pilot study. Arch Womens Ment Health 16: 325-332, 2013.
279. Reddy NV and Omkarappa DB: Cognitive-behavioral therapy for depression among menopausal woman: A randomized controlled trial. J Fam Med Prim Care 8: 1002-1006, 2019.
280. Donegan E, Frey BN, McCabe RE, Streiner DL, Fedorkow DM, Furtado M and Green SM: Impact of the CBT-Meno protocol on menopause-specific beliefs, dysfunctional attitudes, and coping behaviors. Menopause 29: 963-972, 2022.
281. Shabani F, Farvareshi M, Hamdi K, Sadeghzadeh Oskouei B, Montazeri M and Mirghafourvand M: The effect of cognitive-behavioral therapy on stress and anxiety of women with premature ovarian insufficiency: A randomized controlled trial. Post Reprod Health 28: 211-221, 2022.
282. Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R and Krohn MA: Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. Fertil Steril 80: 976-981, 2003.
283. Michopoulos V, Mancini F, Loucks TL and Berga SL: Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: A randomized, controlled trial. Fertil Steril 99: 2084-2091.e1, 2013.
284. Sockalingam S, Leung SE, Ma C, Tomlinson G, Hawa R, Wnuk S, Jackson T, Urbach D, Okrainec A, Brown J, *et al*: Efficacy of telephone-based cognitive behavioral therapy for weight loss, disordered eating, and psychological distress after bariatric surgery: A randomized clinical trial. JAMA Netw Open 6: e2327099, 2023.
285. Rofey DL, Szigethy EM, Noll RB, Dahl RE, Lobst E and Arslanian SA: Cognitive-behavioral therapy for physical and emotional disturbances in adolescents with polycystic ovary syndrome: A pilot study. J Pediatr Psychol 34: 156-163, 2009.
286. Cooney LG, Milman LW, Hantsoo L, Kornfield S, Sammel MD, Allison KC, Epperson CN and Dokras A: Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: A pilot randomized clinical trial. Fertil Steril 110: 161-171.e1, 2018.
287. Ludwig DS and Kabat-Zinn J: Mindfulness in medicine. JAMA 300: 1350-1352, 2008.
288. Grossman P, Niemann L, Schmidt S and Walach H: Mindfulness-based stress reduction and health benefits. A meta-analysis. J Psychosom Res 57: 35-43, 2004.
289. Rosenzweig S, Greeson JM, Reibel DK, Green JS, Jasser SA and Beasley D: Mindfulness-based stress reduction for chronic pain conditions: Variation in treatment outcomes and role of home meditation practice. J Psychosom Res 68: 29-36, 2010.
290. Wong C, Yip BHK, Gao T, Lam KYY, Woo DMS, Yip ALK, Chin CY, Tang WPY, Choy MMT, Tsang KWK, *et al*: Mindfulness-based stress reduction (MBSR) or psychoeducation for the reduction of menopausal symptoms: A randomized, controlled clinical trial. Sci Rep 8: 6609, 2018.
291. Pyri F, Abedi P, Maraghi E and Jefreh M: The effect of mindfulness on quality of life among women with premature ovarian insufficiency: A randomized clinical trial. J Midlife Health 12: 116-121, 2021.
292. Majeed MH, Ali AA and Sudak DM: Mindfulness-based interventions for chronic pain: Evidence and applications. Asian J Psychiatry 32: 79-83, 2018.
293. Kalhori F, Masoumi SZ, Shamsaei F, Mohammadi Y and Yavangi M: Effect of mindfulness-based group counseling on depression in infertile women: Randomized clinical trial study. Int J Fertil Steril 14: 10-6, 2020.
294. Galhardo A, Cunha M and Pinto-Gouveia J: A 7-year follow-up study of the mindfulness-based program for infertility: Are there long-term effects? Clin Psychol Psychother 26: 409-417, 2019.
295. Aalbers S, Fusar-Poli L, Freeman RE, Spreen M, Ket JC, Vink AC, Maratos A, Crawford M, Chen XJ and Gold C: Music therapy for depression. Cochrane Database Syst Rev 11: CD004517, 2017.
296. Koçak DY and Varişoğlu Y: The effect of music therapy on menopausal symptoms and depression: A randomized-controlled study. Menopause 29: 545-552, 2022.
297. Kim S, Kim SM, Hwang H, Kim MK, Kim HJ, Park S and Han DH: The effects of music therapy on the psychological status of women with perimenopause syndrome. Menopause 30: 1045-1052, 2023.
298. Mahmoud MY, Labib K, Sileem SA, Mustafa FA, Hamed WM, Abd Elhamid A, Saleh DM, Alanwar A, Riad AAM, Abdelhakim AM, *et al*: The impact of music therapy on anxiety and pregnancy rate among infertile women undergoing assisted reproductive technologies: A systematic review and meta-analysis. J Psychosom Obstet Gynecol 43: 205-213, 2022.
299. Aba YA, Avci D, Guzel Y, Ozcelik SK and Gurtekin B: Effect of music therapy on the anxiety levels and pregnancy rate of women undergoing in vitro fertilization-embryo transfer: A randomized controlled trial. Appl Nurs Res 36: 19-24, 2017.
300. Domar AD, Gross J, Rooney K and Boivin J: Exploratory randomized trial on the effect of a brief psychological intervention on emotions, quality of life, discontinuation, and pregnancy rates in in vitro fertilization patients. Fertil Steril 104: 440-451.e7, 2015.
301. Clifton J, Parent J, Seehuus M, Worrall G, Forehand R and Domar A: An internet-based mind/body intervention to mitigate distress in women experiencing infertility: A randomized pilot trial. PLoS One 15: e0229379, 2020.
302. Brinsley J, Schuch F, Lederman O, Girard D, Smout M, Immink MA, Stubbs B, Firth J, Davison K and Rosenbaum S: Effects of yoga on depressive symptoms in people with mental disorders: A systematic review and meta-analysis. Br J Sports Med 55: 992-1000, 2021.
303. Darbandi S, Darbandi M, Khorram Khorshid HR and Sadeghi MR: Yoga can improve assisted reproduction technology outcomes in couples with infertility. Altern Ther Health Med 24: 50-55, 2018.
304. Oron G, Allnutt E, Lackman T, Sokal-Arnon T, Holzer H and Takefman J: A prospective study using hatha yoga for stress reduction among women waiting for IVF treatment. Reprod Biomed Online 30: 542-548, 2015.
305. Valoriani V, Lotti F, Vanni C, Noci MC, Fontanarosa N, Ferrari G, Cozzi C and Noci I: Hatha-yoga as a psychological adjuvant for women undergoing IVF: A pilot study. Eur J Obstet Gynecol Reprod Biol 176: 158-162, 2014.

306. Lu X, Liu L and Yuan R: Effect of the information support method combined with yoga exercise on the depression, anxiety, and sleep quality of menopausal women. Psychiatr Danub 32: 380-388, 2020.
307. Jorge MP, Santaella DF, Pontes IMO, Shiramizu VKM, Nascimento EB, Cabral A, Lemos TM, Silva RH and Ribeiro AM: Hatha yoga practice decreases menopause symptoms and improves quality of life: A randomized controlled trial. Complement Ther Med 26: 128-135, 2016.
308. Frederiksen Y, O'Toole MS, Mehlsen MY, Hauge B, Elbaek HO, Zachariae R and Ingerslev HJ: The effect of expressive writing intervention for infertile couples: a randomized controlled trial. Hum Reprod 32: 391-402, 2017.
309. Hart RJ: Physiological aspects of female fertility: Role of the environment, modern lifestyle, and genetics. Physiol Rev 96: 873-909, 2016.
310. Waldman M, Cohen K, Yadin D, Nudelman V, Gorfil D, Laniado-Schwartzman M, Kornwoski R, Aravot D, Abraham NG, Arad M and Hochhauser E: Regulation of diabetic cardiomyopathy by caloric restriction is mediated by intracellular signaling pathways involving 'SIRT1 and PGC-1α'. Cardiovasc Diabetol 17: 111, 2018.
311. Bordone L and Guarente L: Calorie restriction, SIRT1 and metabolism: Understanding longevity. Nat Rev Mol Cell Biol 6: 298-305, 2005.
312. Levine B and Kroemer G: Autophagy in the pathogenesis of disease. Cell 132: 27-42, 2008.
313. Selesniemi K, Lee HJ, Muhlhauser A and Tilly JL: Prevention of maternal aging-associated oocyte aneuploidy and meiotic spindle defects in mice by dietary and genetic strategies. Proc Natl Acad Sci USA 108: 12319-12324, 2011.
314. Smits A, Marei WFA, Moorkens K, Bols PEJ, De Neubourg D and Leroy JLMR: Obese outbred mice only partially benefit from diet normalization or calorie restriction as preconception care interventions to improve metabolic health and oocyte quality. Hum Reprod 37: 2867-2884, 2022.
315. Mishina T, Tabata N, Hayashi T, Yoshimura M, Umeda M, Mori M, Ikawa Y, Hamada H, Nikaido I and Kitajima TS: Single-oocyte transcriptome analysis reveals aging-associated effects influenced by life stage and calorie restriction. Aging Cell 20: e13428, 2021.
316. Słuczanowska-Głąbowska S, Laszczyńska M, Piotrowska K, Grabowska M, Grymuła K and Ratajczak MZ: Caloric restriction increases ratio of estrogen to androgen receptors expression in murine ovaries-potential therapeutic implications. J Ovarian Res 8: 57, 2015.
317. Sharov AA, Falco G, Piao Y, Poosala S, Becker KG, Zonderman AB, Longo DL, Schlessinger D and Ko MSh: Effects of aging and calorie restriction on the global gene expression profiles of mouse testis and ovary. BMC Biol 6: 24, 2008.
318. Garcia DN, Saccon TD, Pradiee J, Rincón JAA, Andrade KRS, Rovani MT, Mondadori RG, Cruz LAX, Barros CC, Masternak MM, *et al*: Effect of caloric restriction and rapamycin on ovarian aging in mice. Geroscience 41: 395-408, 2019.
319. Isola JVV, Zanini BM, Hense JD, Alvarado-Rincón JA, Garcia DN, Pereira GC, Vieira AD, Oliveira TL, Collares T, Gasperin BG, *et al*: Mild calorie restriction, but not 17α-estradiol, extends ovarian reserve and fertility in female mice. Exp Gerontol 159: 111669, 2022.
320. Liu WJ, Zhang XM, Wang N, Zhou XL, Fu YC and Luo LL: Calorie restriction inhibits ovarian follicle development and follicle loss through activating SIRT1 signaling in mice. Eur J Med Res 20: 22, 2015.
321. Zhou XL, Xu JJ, Ni YH, Chen XC, Zhang HX, Zhang XM, Liu WJ, Luo LL and Fu YC: SIRT1 activator (SRT1720) improves the follicle reserve and prolongs the ovarian lifespan of diet-induced obesity in female mice via activating SIRT1 and suppressing mTOR signaling. J Ovarian Res 7: 97, 2014.
322. Li L, Fu YC, Xu JJ, Lin XH, Chen XC, Zhang XM and Luo LL: Caloric restriction promotes the reserve of follicle pool in adult female rats by inhibiting the activation of mammalian target of rapamycin signaling. Reprod Sci 22: 60-67, 2015.
323. Smits A, Marei WFA, De Neubourg D and Leroy JLMR: Diet normalization or caloric restriction as a preconception care strategy to improve metabolic health and oocyte quality in obese outbred mice. Reprod Biol Endocrinol 19: 166, 2021.
324. Chen G, Xie W, Nah J, Sauvat A, Liu P, Pietrocola F, Sica V, Carmona-Gutierrez D, Zimmermann A, Pendl T, *et al*: 3,4-Dimethoxychalcone induces autophagy through activation of the transcription factors TFE3 and TFEB. EMBO Mol Med 11: e10469, 2019.
325. Kepp O, Chen G, Carmona-Gutierrez D, Madeo F and Kroemer G: A discovery platform for the identification of caloric restriction mimetics with broad health-improving effects. Autophagy 16: 188-189, 2020.
326. Zhang H, Ni W, Yu G, Geng Y, Lou J, Qi J, Chen Y, Li F, Ye H, Ma H, *et al*: 3,4-Dimethoxychalcone, a caloric restriction mimetic, enhances TFEB-mediated autophagy and alleviates pyroptosis and necroptosis after spinal cord injury. Theranostics 13: 810-832, 2023.
327. Jafari M, Macho-González A, Diaz A, Lindenau K, Santiago-Fernández O, Zeng M, Massey AC, de Cabo R, Kaushik S and Cuervo AM: Calorie restriction and calorie-restriction mimetics activate chaperone-mediated autophagy. Proc Natl Acad Sci USA 121: e2317945121, 2024.
328. Sciarretta S, Forte M, Castoldi F, Frati G, Versaci F, Sadoshima J, Kroemer G and Maiuri MC: Caloric restriction mimetics for the treatment of cardiovascular diseases. Cardiovasc Res 117: 1434-1449, 2021.
329. Pallauf K, Günther I, Kühn G, Chin D, de Pascual-Teresa S and Rimbach G: The potential of resveratrol to act as a caloric restriction mimetic appears to be limited: Insights from studies in mice. Adv Nutr 12: 995-1005, 2021.
330. Pernicova I and Korbonits M: Metformin-mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol 10: 143-156, 2014.
331. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M and Andreelli F: Cellular and molecular mechanisms of metformin: An overview. Clin Sci (Lond) 122: 253-270, 2012.
332. Masoudi FA, Wang Y, Inzucchi SE, Setaro JF, Havranek EP, Foody JM and Krumholz HM: Metformin and thiazolidinedione use in medicare patients with heart failure. JAMA 290: 81-85, 2003.
333. Valencia WM, Palacio A, Tamariz L and Florez H: Metformin and ageing: Improving ageing outcomes beyond glycaemic control. Diabetologia 60: 1630-1638, 2017.
334. Morales DR and Morris AD: Metformin in cancer treatment and prevention. Annu Rev Med 66: 17-29, 2015.
335. Qin X, Du D, Chen Q, Wu M, Wu T, Wen J, Jin Y, Zhang J and Wang S: Metformin prevents murine ovarian aging. Aging (Albany NY) 11: 3785-3794, 2019.
336. Huang CC, Chou CH, Yang YS, Ho HN, Shun CT, Wen WF, Chen SU and Chen MJ: Metformin: A novel promising option for fertility preservation during cyclophosphamide-based chemotherapy. Mol Hum Reprod 27: gaaa084, 2021.
337. Cao Y, Wang Z, Zhang C, Bian Y, Zhang X, Liu X, Chen W and Zhao Y: Metformin promotes in vitro maturation of oocytes from aged mice by attenuating mitochondrial oxidative stress via SIRT3-dependent SOD2ac. Front Cell Dev Biol 10: 1028510, 2022.
338. Ayhan S, Hancerliogullari N, Guney G, Gozukucuk M, Caydere M, Guney SS, Tokmak A and Ustun Y: Does the addition of metformin to carboplatin treatment decreases ovarian reserve damage associated with carboplatin usage? J Ovarian Res 16: 184, 2023.
339. Landry DA, Yakubovich E, Cook DP, Fasih S, Upham J and Vanderhyden BC: Metformin prevents age-associated ovarian fibrosis by modulating the immune landscape in female mice. Sci Adv 8: eabq1475, 2022.
340. Gambini J, Inglés M, Olaso G, Lopez-Grueso R, Bonet-Costa V, Gimeno-Mallench L, Mas-Bargues C, Abdelaziz KM, Gomez-Cabrera MC, Vina J and Borras C: Properties of resveratrol: In vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxid Med Cell Longev 2015: 837042, 2015.
341. Rajman L, Chwalek K and Sinclair DA: Therapeutic potential of NAD-boosting molecules: The in vivo evidence. Cell Metabv 27: 529-547, 2018.
342. Côté CD, Rasmussen BA, Duca FA, Zadeh-Tahmasebi M, Baur JA, Daljeet M, Breen DM, Filippi BM and Lam TK: Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. Nat Med 21: 498-505, 2015.
343. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, Hoeks J, van der Krieken S, Ryu D, Kersten S, *et al*: Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab 14: 612-622, 2011.
344. Battaglia R, Caponnetto A, Caringella AM, Cortone A, Ferrara C, Smirni S, Iannitti R, Purrello M, D'Amato G, Fioretti B and Di Pietro C: Resveratrol treatment induces mito-miRNome modification in follicular fluid from aged women with a poor prognosis for in vitro fertilization cycles. Antioxidants (Basel) 11: 1019, 2022.

345. Li R, Li E, Kamili G, Ou S and Yang D: Effect of resveratrol on superovulation in mice. Biomed Pharmacother 146: 112565, 2022.
346. Gou M, Li J, Yi L, Li H, Ye X, Wang H, Liu L, Sun B, Zhang S, Zhu Z, *et al*: Reprogramming of ovarian aging epigenome by resveratrol. PNAS Nexus 2: pgac310, 2022.
347. Wu H, Xue J, Di H, Lv C, Hao Y and Nie Z: Resveratrol improves ovarian function in aged rat by inhibiting oxidative stress and activating the Sirt1. Gen Physiol Biophys 41: 53-61, 2022.
348. Zhou J, Xue Z, He HN, Liu X, Yin SY, Wu DY, Zhang X, Schatten H and Miao YL: Resveratrol delays postovulatory aging of mouse oocytes through activating mitophagy. Aging (Albany NY) 11: 11504-11519, 2019.
349. Liang QX, Lin YH, Zhang CH, Sun HM, Zhou L, Schatten H, Sun QY and Qian WP: Resveratrol increases resistance of mouse oocytes to postovulatory aging in vivo. Aging (Albany NY) 10: 1586-1596, 2018.
350. Liu MJ, Sun AG, Zhao SG, Liu H, Ma SY, Li M, Huai YX, Zhao H and Liu HB: Resveratrol improves in vitro maturation of oocytes in aged mice and humans. Fertil Steril 109: 900-907, 2018.
351. Okamoto N, Sato Y, Kawagoe Y, Shimizu T and Kawamura K: Short-term resveratrol treatment restored the quality of oocytes in aging mice. Aging (Albany NY) 14: 5628-5640, 2022.
352. Sun YL, Tang SB, Shen W, Yin S and Sun QY: Roles of resveratrol in improving the quality of postovulatory aging oocytes in vitro. Cells 8: 1132, 2019.
353. Cai M, Sun H, Huang Y, Yao H, Zhao C, Wang J and Zhu H: Resveratrol protects rat ovarian luteinized granulosa cells from H_2O_2-induced dysfunction by activating autophagy. Int J Mol Sci 24: 10914, 2023.
354. Moreira-Pinto B, Costa L, Felgueira E, Fonseca BM and Rebelo I: Low doses of resveratrol protect human granulosa cells from induced-oxidative stress. Antioxidants (Basel) 10: 561, 2021.
355. Pruessner M, Hellhammer DH, Pruessner JC and Lupien SJ: Self-reported depressive symptoms and stress levels in healthy young men: Associations with the cortisol response to awakening. Psychosom Med 65: 92-99, 2003.
356. Campagne DM: Should fertilization treatment start with reducing stress? Hum Reprod 21: 1651-1658, 2006.
357. Obayashi K: Salivary mental stress proteins. Clin Chim Acta 425: 196-201, 2013.
358. Shah K, Kumari R and Jain M: Unveiling stress markers: A systematic review investigating psychological stress biomarkers. Dev Psychobiol 66: e22490, 2024.
359. Lavalle S, Masiello E, Iannella G, Magliulo G, Pace A, Lechien JR, Calvo-Henriquez C, Cocuzza S, Parisi FM, Favier V, *et al*: Unraveling the complexities of oxidative stress and inflammation biomarkers in obstructive sleep apnea syndrome: A comprehensive review. Life (Basel) 14: 425, 2024.
360. Ok J, Park S, Jung YH and Kim T: Wearable and implantable cortisol-sensing electronics for stress monitoring. Adv Mater 36: 2211595, 2024.
361. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ and Moran LJ: Depression, anxiety and perceived stress in women with and without PCOS: A community-based study. Psychol Med 49: 1510-1520, 2019.
362. Tay CT, Teede HJ, Hill B, Loxton D and Joham AE: Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: A community-based cohort study. Fertil Steril 112: 353-361, 2019.
363. Rowlands IJ, Teede H, Lucke J, Dobson AJ and Mishra GD: Young women's psychological distress after a diagnosis of polycystic ovary syndrome or endometriosis. Hum Reprod 31: 2072-2081, 2016.