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Opinion

Trauma and female reproductive health across the lifecourse: motivating a research agenda for the future of women's health

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ABSTRACT

The aetiology behind many female reproductive disorders is poorly studied and incompletely understood despite the prevalence of such conditions and substantial burden they impose on women's lives. In light of evidence demonstrating a higher incidence of trauma exposure in women with many such disorders, we present a set of interlinked working hypotheses proposing relationships between traumatic events and reproductive and mental health that can define a research agenda to better understand reproductive outcomes from a trauma-informed perspective across the lifecourse. Additionally, we note the potential for racism to act as a traumatic experience, highlight the importance of considering the interaction between mental and reproductive health concerns, and propose several neuroendocrinological mechanisms by which traumatic experiences might increase the risk of adverse health outcomes in these domains. Finally, we emphasize the need for future primary research investigating the proposed pathways between traumatic experiences and adverse female reproductive outcomes.

Keywords: mental health / trauma / stress / infertility / premenstrual dysphoric disorder / pregnancy complications / lifecourse / female reproductive health

Introduction

Female reproductive health conditions such as endometriosis, premenstrual dysphoric disorder (PMDD), and infertility have a substantial impact on women's quality of life. The mechanisms causing them and intervention strategies to treat them are incompletely understood (Ortiz, 2008; Howard, 2009; Stratton and Berkley, 2011; Craner *et al.*, 2014; Sadeghi, 2015). Unfortunately, without knowing the underlying causes of adverse reproductive health and effective treatments, many women endure a lifetime of suffering. The prevalence of female reproductive health conditions and difficulties is staggering; chronic pelvic pain (i.e., pelvic pain lasting at least 6 months that does not vary with one's menstrual cycle), for instance, was estimated to affect up to 24% of women, and dysmenorrhea (i.e., severe pain due to menstrual cramps) was estimated to affect an overwhelming majority (81%) of women (Latthe *et al.*, 2006). One in five women will struggle with infertility, yet the underlying cause is unexplained in more than 40% of cases (Cates *et al.*, 1985; Smith *et al.*, 2003). The limited understanding of the underlying disease pathways that lead to adverse reproductive outcomes results in poor prevention and treatment options being available to women.

Mental health disorders are common in the general population, affecting roughly one in five individuals in USA (National Institute of Mental Health, 2022), and a subset of women who suffer from adverse reproductive disorders would be expected to have comorbid mental health conditions. As evidence of this, women with reproductive problems often express feelings suggesting considerable psychological malaise, such as having 'an inner war' or being 'snapped in two' (Inhorn and Whittle, 2001; McGowan *et al.*, 2007; Verdonk *et al.*, 2009; Osborn *et al.*, 2020). Women who struggle with conditions such as PMDD, endometriosis, and infertility have a lower quality of life than other women

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(El-Masry and Abdelfatah, 2012; Facchin et al., 2015; Kitchen et al., 2017). Infertile women report a high prevalence of anxiety (15–76%) and depression (18–56%), and 9% report experiencing suicidal thoughts or behaviours (Chiaffarino et al., 2011; Rooney and Domar, 2018). In sum, reproductive health disorders have a substantial impact on mental health and may trigger new concerns or exacerbate existing ones.

Sexual assault, intimate partner violence, physical abuse, and nonphysical trauma (e.g., neglect, traumatic loss, household dysfunction, childhood maltreatment) have been associated with adverse reproductive endpoints (Girdler et al., 2003; Harris et al., 2018; Merrick et al., 2020; Schweizer-Schubert et al., 2021; Rieder et al., 2022). For instance, in a prospective cohort study of 1251 adolescents and young adults, Perkonigg et al. (2004) found that traumatic events increased women's risk of developing PMDD 4-fold (odds ratio (OR) = 4.2; 95% confidence interval (CI): 1.2, 12.0). Given the alarmingly high prevalence of traumatic events (e.g. 70% in one large-scale, international study), additional epidemiologic research is needed to determine how trauma may be associated with and potentially causally linked to adverse female reproductive health (Benjet et al., 2016).

To further complicate the relationship, traumatic exposures may increase the risk of adverse reproductive outcomes not only directly, but also through an indirect pathway via mental health. Poor mental health resulting from traumatic experiences are thought to further increase women's risk of developing reproductive disorders and/or exacerbate pre-existing conditions (Braveman and Barclay, 2009; Alwin, 2012; Campbell et al., 2018). Since reproductive disorders commonly provoke distress, mental and reproductive endpoints likely have synergistic, interactive and/or additive effects that serve to perpetuate the vicious cycle of exposure and disease (Born et al., 2005; Lynch et al., 2014; Choi, et al., 2015; Rooney and Domar, 2018). Indeed, those reproductive health concerns strikingly identified by pain (e.g., PMDD, pelvic pain, dysmenorrhea, among others) may very well be somatic embodiments of underlying trauma (Stein et al., 2004; Zuckerman et al., 2018; Iloson et al., 2021). We hypothesized that traumatic life events are an important and overlooked cause of adverse reproductive outcomes (van der Kolk, 2003; Fratto, 2016), and aimed to develop a preliminary framework describing the association between trauma and adverse female reproductive health outcomes and investigate the biological plausibility of such a relationship by conducting a manual review of the existing literature. Our goal was to call attention to the need for further research on this topic and provide a set of working hypotheses that might guide future investigations. Addressing the underrecognized needs of women starts with contributing evidence of the risk factors and mechanisms of adverse reproductive health. Although we will explore these questions from the lens of PMDD, for which there has been comparatively more research on this topic, similar arguments may be made for other underresearched reproductive conditions and infertility diagnoses.

What evidence supports an association between trauma and adverse female reproductive outcomes?

Several biological and socio-behavioural consequences of traumatic exposure have been proposed to contribute to adverse reproductive health outcomes. Baral et al. (2013) proposed the following three consequences: (i) transmission of sexually transmitted infections (STIs), (ii) impacts of sexually transmitted infection if it is left untreated, or is recurrent or incurable, and (iii) manifestations of trauma upon sexual health outcomes and behaviours. A large portion of the literature on this subject has focused on the first two pathways identified. For example, Leblanc et al. (2020), in a cross-sectional, ecologic study of 279 women between the ages of 19 and 64 years, found that childhood sexual trauma predicted an increase in the number of lifetime STIs ($P < 0.001$). The authors additionally found that lifetime incidence of trading sex for survival resources was predicted by the number and severity of lifetime stressors ($P < 0.001$), severity of intimate partner violence ($P < 0.001$),and severity of childhood emotional abuse ($P < 0.001$). Similarly, Mota et al. (2019), in a cross-sectional study of 36 909 US adults, found that individuals with a lifetime history of PTSD were 54% more likely to have contracted an STI in the preceding year than those with no history of a PTSD diagnosis (adjusted odds ratio (AOR) = 1.54, 95% CI: 1.04, 2.28, $P < 0.05$). Yet, considerably less research has been afforded to the third pathway which considers how emotional responses to trauma can affect sexual and reproductive health. Physical and sexual abuse in childhood have respectively been associated with a 10% (hazard ratio (HR) = 1.10, 95% CI: 1.01, 1.20) and 15% (HR = 1.15, 95% CI: 1.03, 1.30) increased risk of laparoscopically confirmed endometriosis in adulthood (Harris et al., 2018). Similarly, several studies support a significant association between trauma and moderate-severe premenstrual syndrome (PMS) and PMDD (Golding et al., 2000). For example, in a prospective-longitudinal survey study of 1488 adolescents and young adults, Wittchen et al., (2003) found that those who met the criteria for PTSD were almost 12 times (OR = 11.7, 95% CI: 3.0, 46.2) more likely to meet the criteria for PMDD. Likewise, a case–control study of 56 reproductive-aged women reported that those with a history of abuse were 4.5 times (OR = 4.5, 95% CI: 1.46, 13.89) more likely to have PMDD (Girdler et al., 2003). Evidence from the trauma literature strongly supports a pathway via behavioural changes: trauma is associated with substantially increased risk of any eating disorder, with sexual trauma having the highest increase in risk (AOR = 4.32, 95% CI: 3.58, 5.21; Convertino et al., 2022), as well as a 41% increase in risk of substance use disorders (95% CI: 1.24–1.60; LeTendre and Reed, 2017). Additionally, women who have experienced trauma are less likely to access preventative forms of care such as cervical and breast cancer screening, potentially due to prior experiences or fear of insensitive or mysoginistic clinical practice (American College of Obstetricians and Gynecologists (ACOG), 2021). However, our lack of knowledge regarding the biological mechanisms by which mental health-related pathways might influence reproductive disorders marks a glaring gap in our current understanding of female reproduction from a lifecourse perspective (Demyttenaere et al., 1988; Lapane et al., 1995; Lynch et al., 2014).

Apart from gynaecological disorders, traumatic life experiences have also been found to influence fertility and pregnancy outcomes. A prospective cohort study of 742 women between the ages of 18 and 45 years reported that each adverse childhood event experienced was associated with a 9% (relative risk ratio (RR) = 1.09, 95% CI: 1.05, 1.13) increase in the risk of fertility difficulties and a 32% (RR = 1.32, 95% CI: 1.08, 1.62) and a 3% (fecundability ratio (FR) = 0.97, 95% CI: 0.94, 0.99) decrease in fecundability (i.e., probability of conception in one menstrual cycle; Jacobs et al., 2015). Similarly, a cross-sectional study of 246 trauma-exposed women between the ages of 19 and 59 years found that increases in posttraumatic stress symptoms predicted an increase in time to conception ($P = 0.01$; Wamser-Nanney, 2020). Among women who can become pregnant, trauma has been strongly associated with postpartum stress symptoms. A

retrospective cohort study of 198 women who had just given birth found that a history of two or more traumatic life events increased one's risk of high postpartum posttraumatic stress by 3-fold (OR = 4.0, 95% CI: 1.2, 8.3, $P = 0.01$; Cohen *et al.*, 2004). Furthermore, a cross-sectional study by Seng *et al.* (2010) comparing pregnant women ($n = 1581$) and women from the general population ($n = 2000$) found that, compared to trauma-exposed controls, trauma-exposed pregnant women were nearly 3.4 times (RR = 3.38, 95% CI: 2.14, 5.35) more likely to meet the criteria for PTSD. This is particularly concerning given that maternal PTSD has been reported to increase the risk of preterm birth by 35% (AOR = 1.35, 95% CI: 1.14, 1.61; Shaw *et al.*, 2014). Moreover, research suggests that trauma-exposed women experience more PTSD symptoms and psychological distress during the late luteal phase of the menstrual cycle (i.e., phase during which PMDD symptoms are experienced), as exemplified by a prospective cohort study that found a substantial increase in posttraumatic symptom severity during the midluteal phase ($P = 0.038$; Nillni *et al.*, 2015; see also Rieder *et al.*, 2022).

The picture becomes even more complex once we consider the bi-directional relationship between emotional and reproductive health due to trauma. Adverse reproductive health significantly increases the risk of experiencing distress; a prospective survey study found that women who experienced pregnancy loss were 4.4 times more likely than pregnant controls to report moderate/severe anxiety symptoms (OR = 4.4, 95% CI: 0.94, 20.67) and 8.24 times more likely to report moderate/severe posttraumatic stress symptoms (OR = 8.24, 95% CI: 1.04, 65.37; Farren *et al.*, 2016). Additionally, a prospective cohort study of 2146 women trying to conceive found that baseline moderate to severe depressive symptoms decreased fecundability by almost 40% (FR = 0.62, 95% CI: 0.43, 0.91; Nillni *et al.*, 2016). Another prospective cohort study by Demyttenaere *et al.* (1988) reported that pregnant women who experienced pregnancy loss had higher trait anxiety (Cohen's $d = 0.76$, 95% CI: 0.1, 1.43, $P < 0.02$) than those who did not, and that higher trait anxiety was associated with requiring more artificial donor insemination cycles for conception ($P < 0.001$).

Moreover, an association between traumatic experiences and increased risk of female reproductive disorders could contribute to explaining the reproductive health disparities between White women and women of colour, particularly Black women in the USA (Prather *et al.*, 2016). For example, a systematic review of 30 studies by Schaaf *et al.* (2013) found that Black women had two times the odds of preterm birth of White women in 2019 (adjusted OR = 2.00, 95% CI: 1.8, 2.2), and a multi-disciplinary working group concluded that institutional- and individual-level racism was the most likely overarching cause (Braveman *et al.*, 2021). Additionally, Black women had 3.55 times the maternal mortality rate (MMR) of White women in 2016–2017 (MMR = 3.55, 95% CI: 2.94, 4.28; MacDorman *et al.*, 2021). As detailed by Carter (2007), previous researchers have conceptualized racism as a form of trauma that contributes to psychological health disparities across racial groups. In addition to disparities in access and quality of healthcare and socioeconomic status due to institutional racism, chronic stress resulting from racial trauma might directly increase Black women's risk of reproductive health consequences (Prather *et al.*, 2016).

However, not all studies support an effect of psychiatric variables on reproductive outcomes. For example, the aforementioned cross-sectional study by Wamser-Nanney (2020) found no evidence for an association between trauma history and time to conception ($P = 0.1$) or self-reported infertility (OR = 1.01, $P = 0.21$), nor between posttraumatic stress symptoms and infertility (OR = 0.98, $P = 0.72$). However, the authors caution that the use of convenience sampling of undergraduate students and Amazon Mechanical Turk workers, the assessment of all variables via retrospective self-report, and the failure to consider potential confounders (e.g., body mass index, substance use) may have contributed to their null findings. In addition, a cross-sectional study of 339 reproductive-aged women failed to find a statistically significant association between past depressive symptoms and infertility (AOR = 1.7, 90% CI: 0.9, 3.2), a finding that might be explained by their inability to control for excessive alcohol use and the use of short, retrospective self-report measures to capture all variables at a single time-point (Lapane *et al.*, 1995). However we do note that the point estimate of 1.7 is meaningfully elevated, and the small sample likely resulted in imprecision and wide confidence intervals; a power analysis indicated that, even assuming that other covariates, which included history of STIs, alcohol use and BMI, accounted for only 10% of the variance in infertility, a sample size of over 700 would have been necessary to have 80% power to detect the observed OR. Moreover, a meta-analysis of 14 studies by Boivin *et al.* (2011) found no meaningful difference in preconception emotional distress between individuals who were and were not successful in their first cycle of assisted reproductive technologies (ART; $P = 0.3$), although the authors note that not all studies included assessed the comparability of the pregnant and not pregnant groups on potential confounders and they suggest that the effect of stress might only be evident over multiple treatment cycles. Additionally, in light of substantial evidence that stress increases the probability of discontinuing treatment (e.g., Pedro *et al.*, 2017), their finding might be explained by a higher rate of attrition among couples who experienced the most distress. It is important to note, however, that it is similarly possible that studies that have found an effect of emotional distress on ART and that have failed to consider the number of treatment cycles completed in their analysis would be subject to the same differential attrition bias. Similarly, a prospective cohort study of 202 women beginning their first cycle of *in vitro* fertilization (IVF) found no statistically significant mean difference in preconception depression (Hedges' $g = -0.11$, 95% CI: −0.42, 0.19) or anxiety (Hedges' $g = -0.12$, 95% CI: −0.43, 0.18) between those who got pregnant and those who did not (Pasch *et al.*, 2012). Nevertheless, the relatively small sample size, the failure to consider potential confounders such as age, duration of infertility, infertility diagnosis, BMI, etc., and the investigation of only the first cycle of IVF may have biased their results towards the null. Finally, to the best of our knowledge there has yet to be an investigation of associations between PMDD and adverse reproductive outcomes and this remains a major gap in the evidence. In sum, the literature posits tentative but inadequately studied associations between mental and reproductive health, and the inconsistency in findings necessitate future, well-designed prospective research investigating the proposed pathway.

In light of the studies reviewed above, the biological and psychological consequences stemming from trauma might continue to exert their effects far beyond the initial exposure or window of vulnerability. Indeed, specific adverse reproductive outcomes, such as miscarriage, have been linked to the development of PTSD and may serve as independent traumatic exposures that further increase one's risk of developing mental health problems (Born *et al.*, 2005). Such a cyclical model has previously been posed by Taymor and Bresnick (1979), who hypothesized that stress, quality of life and female fertility operate in a vicious cycle. More specifically, their model proposes three main ways in

which emotional health is related to fertility: (i) primary emotional factors and their underlying neurobiology are contributors to infertility; (ii) emotional factors are consequences of infertility; and (iii) there are additional emotional tensions introduced by medical tests and treatment failures (Taymor and Bresnick, 1979). Social factors such as familial and societal expectations, attitudes, and support have also been reported to influence the relationship between infertility and adverse mental health outcomes, potentially explaining some of the individual and cross-cultural variation in how such a cycle might play out (Hasanpour et al., 2014; Roberts et al., 2020).

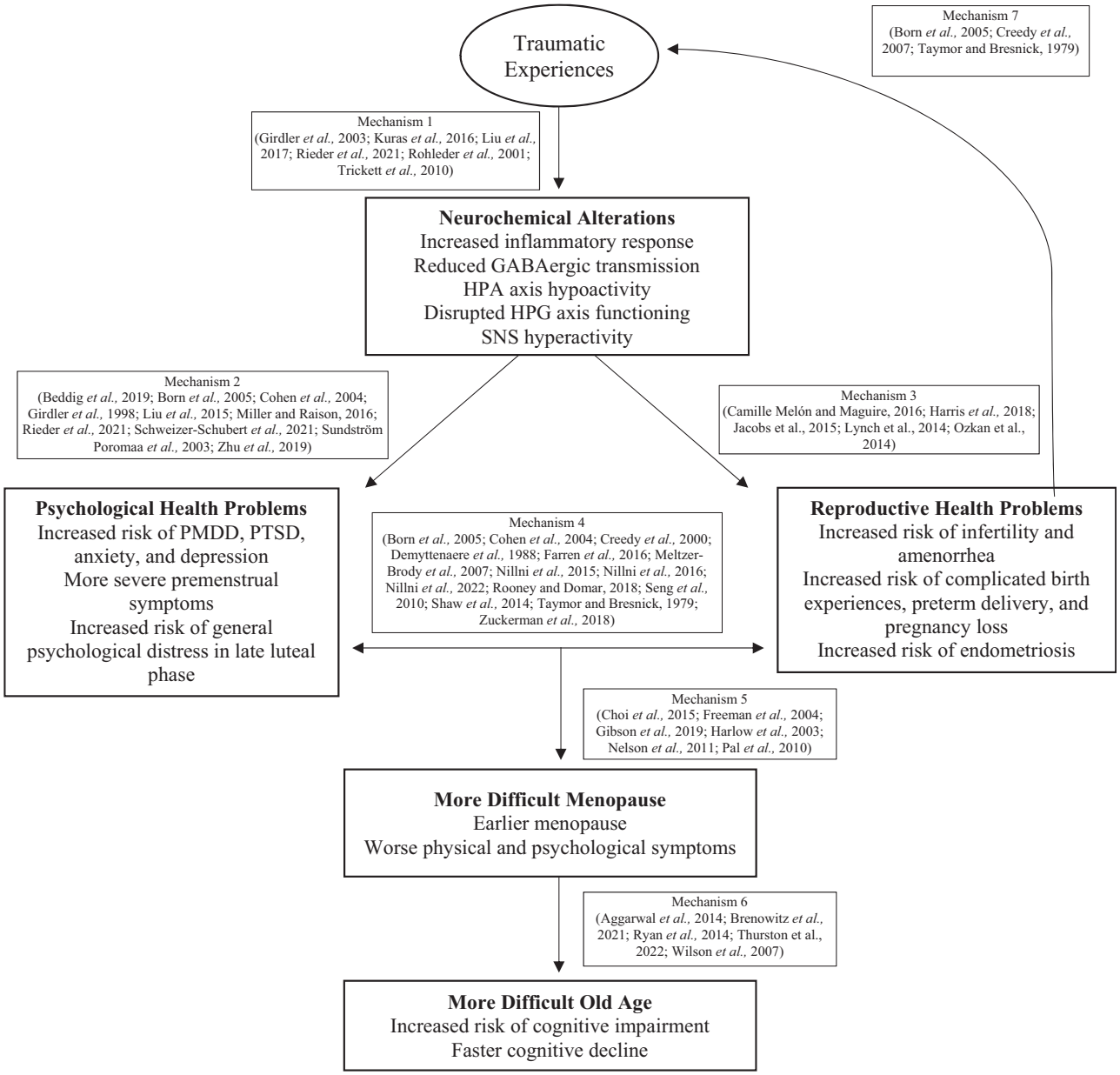
Compounding matters, mental and reproductive health problems may have negative implications far beyond a woman's fertile years. Trauma history, infertility, and PMS have all been associated with more severe menopausal symptomology (Freeman et al., 2004; Nelson et al., 2011; Gibson et al., 2019). For instance, in a multivariable regression model presented by Gibson et al. (2019), women with symptoms of PTSD were 3.02 times more likely to have difficulty sleeping (OR = 3.02, 95% CI: 2.22, 4.09) and more likely to present with multiple vasomotor symptoms and vaginal symptoms. Additionally, in a prospective cohort story of 291 premenopausal women, infertility increased the risk of experiencing decreased libido (OR = 1.86, 95% CI: 1.05, 3.31) and vaginal dryness (OR = 1.79, 95% CI: 1.19, 6.94). Stress has also been associated with an earlier transition to menopause; a cross-sectional study by Pal et al. (2010) found that infertile women who reported chronic psychosocial stress were almost 3.3 times (OR = 3.25, 95% CI: 1.16, 9.11) more likely to be diagnosed with diminished ovarian reserve. A prospective cohort study of 976 premenopausal women found that those with high baseline depression were twice as likely (HR = 2.0, 95% CI: 1.3, 3.0) to begin perimenopause over the course of the 36-month study (Harlow et al., 2003). Many of these associations translate to an increased risk of the development of cognitive impairment and faster cognitive decline. Specifically, Ryan et al. (2014) found that women who began menopause before the age of 40 years were 35% more likely (HR = 1.35, 95% CI: 1.05, 1.74) to display a decline in global cognitive function over the 7-year study. Similarly, Brenowitz et al. (2021) reported that having experienced depressive symptoms in early adulthood was associated with a 59% increased risk of cognitive impairment (OR = 1.59, 95% CI: 1.35, 1.87) and a 77% higher risk of depressive symptoms in later adulthood (OR = 1.77, 95% CI: 1.42, 2.21); both outcomes were associated with faster rates of cognitive decline than in those with no history of depression. Further, Thurston et al. (2022) found that among 145 women between the ages of 45 and 67 years, a history of trauma exposure predicted greater volume of white matter hyperintensities ($P < 0.05$), an early indicator of increased risk of later cognitive decline, dementia, and stroke.

Cumulatively, much of the current literature suggests that the link between reproductive and emotional health instigated by trauma may have severe consequences for a woman's wellbeing throughout every life stage. Reproductive health problems can arise from a complex interplay between mind, body, and environmental factors. Social and environmental exposures that a woman experiences throughout her life provide clues as to the ways in which her mind and body react to the world around her. Developing an understanding underpinned by a conceptual framework of how traumatic events might contribute to the risk of developing adverse endpoints helps uncover the reproductive, neurobiological, psychological, and social pathways involved. Figure 1 summarizes the conceptual framework described above. This framework presents a set of working hypotheses that serve to guide future research investigating reproductive outcomes across the lifecourse by providing a trauma-informed perspective. Table 1 summarizes the evidence informing this framework.

What neuroendocrinological consequences of trauma might affect reproductive and mental health?

Two neuroendocrinological systems primarily govern the body's response to stressors: the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. There is evidence for altered activity in both systems following trauma and in reproductive health disorders. For example, a small prospective cohort study by Rieder et al. (2022; $n = 40$) found that the luteal menstrual phase (i.e., the days immediately preceding menstruation, characterized by a sudden drop in levels of estradiol and progesterone) was positively correlated with increased SNS reactivity as measured by salivary alpha-amylase (Pearson correlation coefficient (r) = 0.35, $P = 0.029$). Moreover, a case–control study by Girdler et al. (2003) found that women diagnosed with PMDD ($n = 20$) who have a history of trauma showed greater reactivity of the β1 and β2 adreno-receptors during both the luteal and follicular phases than those without abuse histories ($n = 8$) when exposed to stress. High levels of salivary alpha-amylase have been associated with up to a 29% decrease in fecundity (FR = 0.71, 95% CI: 0.51, 1.00) and a 2-fold increase (RR = 2.07, 95% CI: 1.04, 4.11) in risk of infertility (Lynch et al., 2014). However, a prospective cohort study of 337 women pregnant women found that preconception basal salivary cortisol (adjusted HR = 0.72, 95% CI: 0.43, 1.19) and alpha-amylase concentrations (adjusted HR = 1.01, 95% CI: 0.59, 1.72) were not associated with pregnancy loss (Lynch et al., 2018). They caution, however, that participants in their study appeared to be, on average, less stressed than the general population, and therefore may have been less likely to experience early pregnancy loss related to stress, and that cortisol was assessed by only two saliva samples taken by the participants at home prior to pregnancy, and that this collection method has shown to be less accurate than taking multiple measurements during the day (Lynch et al., 2018). Further, the timing of salivary cortisol measurement may not have been in the sensitive or vulnerable window relative to the outcome. Despite these inconsistent findings, there is growing evidence in support of the hypothesis that trauma increases the brain's reactivity to norepinephrine partly via alterations at the level of the adreno-receptors, as has been suggested in previous research on trauma (e.g., Hendrickson et al., 2018).

There is also evidence of an altered HPA-axis activity after trauma and with reproductive health disorders. A case–control study of 24 women (PMDD: $n = 12$) by Girdler et al. (1998) found that women with PMDD and self-reported histories of trauma had significantly lower cortisol levels than healthy controls both at rest and following exposure to a stressor. Another case–control study by Beddig et al. (2019) similarly found that the cortical awakening response peaked 15 min later in women with PMDD than in healthy controls, supporting hypotheses of a blunted HPA-axis activity in this population. Similar results have been found in trauma-exposed women without a diagnosis of PMDD, indicating that the HPA axis hypoactivity following trauma exposure is not specific to psychiatric disorders (Trickett et al., 2010; Rieder et al., 2022). Furthermore, changes in cortisol levels have been found to interfere with the hypothalamic–pituitary–gonadal (HPG) axis, which secretes reproductive hormones (i.e., follicle stimulating hormone and luteinizing hormone) that drive major



GABA: γ-aminobutyric acid
HPA: hypothalamic-pituitary-adrenal
HPG: hypothalamic-pituitary-gonadal
SNS: sympathetic nervous system
PMDD: premenstrual dysphoric disorder
PTSD: posttraumatic stress disorder

Figure 1. Conceptual framework for the influence of traumatic experiences on female reproductive and mental health across the lifecourse. GABA, γ-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; SNS, sympathetic nervous system; PMDD, premenstrual dysphoric disorder; PTSD, posttraumatic stress disorder.

reproductive events (e.g., development, puberty, menstruation; Samuels *et al.*, 1994; Ball and Balthazart, 2002). Therefore, dysregulation of the HPA-axis presents a significant concern and a putative pathway linking trauma to adverse reproductive endpoints, including infertility, with diffuse aetiologic origins.

A decrease in the transmission of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter and a critical modulator of HPA axis activity, may be another contributing mechanism. More specifically, GABA upregulates HPA axis activity during times of acute stress and inhibits it when such a response is not necessary (Camille Melón and Maguire, 2016). A full discussion of the mechanisms by which trauma exposure may decrease GABAergic activity is beyond the scope of this article. However, briefly stated, epigenetic changes in response to trauma may increase the inflammatory response to stressors, which in turn activates a cascade of signalling mechanisms that increase the glutamatergic tone and thus decrease levels of brain-derived neurotropic factor (BDNF) (Girdler *et al.*, 1998; O'Brien *et al.*, 2007; Cubeddu *et al.*, 2011; Miller and Raison, 2016; Zannas *et al.*, 2019). More specifically, Miller and Raison (2016) proposed that pro-

Table 1. Evidence supporting associations between trauma, mental health, reproductive health, menopause and late-life cognitive impairment in women.

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Trauma and adverse reproductive outcomes							
Girdler *et al.* (2003)	Case–Control Study	$n = 56$ reproductive-aged women (PMDD: $n = 28$)	Abuse history	PMDD diagnosis	OR = 4.5 (95% CI: 1.46, 13.89)	$P < 0.001$	– Convenience sampling limits generalizability. – Potentially underpowered due to small sample size. – No effect sizes reported. Insufficient information to calculate effect sizes for five outcomes of primary interest. – Norepinephrine and cortisol measured only once at baseline. – No comparisons between all participants with PMDD versus all women without PMDD or all women with a history of abuse vs. all women without a history of abuse.
Perkonigg *et al.* (2004)	Prospective Cohort Study	$n = 1251$ women aged 14–24 years	Traumatic event exposure		OR = 4.2 (95% CI: 1.2, 12.0)	$P < 0.05$	– PMDD assessed by a retrospective rather than prospective measure, potentially introducing misclassification bias. – Did not consider age at which traumatic event occurred. – Majority of the sample was well-educated and of middle to high socioeconomic status, thus results may not generalize to the general population. – Sample consisted of adolescents and young adults, results may not be generalizable to older women.
			Anxiety disorder at baseline		OR = 2.5 (95% CI: 1.1, 5.5)	$P < 0.05$	
			Daily hassles	PMDD diagnosis	OR = 1.6 (95% CI: 1.1, 2.3)	$P < 0.05$	
			PTSD diagnosis at baseline		OR = 0.7 (95% CI: 0.1, 2.8)	$P > 0.05$	
Harris *et al.* (2018)	Prospective Cohort Study	$n = 60\,595$ premenopausal women	Physical abuse		HR = 1.10 (95% CI: 1.01, 1.20)		– All variables assessed via retrospective self-reports, potentially introducing recall and misclassification biases. – Sample consisted of primarily middle-aged, Caucasian nurses, limiting generalizability to the general population.
			Sexual abuse	Laproscopically confirmed endometriosis	HR = 1.15 (95% CI: 1.03, 1.30)		
			Combination of physical and sexual abuse		HR = 1.31 (95% CI: 1.19, 1.45)		
Rieder *et al.* (2022)	Prospective Cohort Study	$n = 40$ reproductive trauma-exposed women aged 18–33 years	Day in follicular phase (low to high estradiol)	Total PTSD symptom severity	$b = -0.39$; SE = 0.19	$P = 0.039$	– Biological measures assessed cross-sectionally rather than longitudinally. – Menstrual cycle phase at assessment estimated based on previous cycles. – Ecological momentary assessment limited to dimensional approach and requires replication in clinical populations.
				Salivary alpha-amylase reactivity	$r = 0.35$	$P = 0.029$	
			Menstrual cycle phase (high- vs. low-estradiol)	Cortisol reactivity	$r = 0.41$	$P = 0.01$	
Kuras *et al.* (2017)	Cross-Sectional Study	$n = 41$ healthy adults aged 18–35 years (Female: $n = 17$)	Childhood adversity	Salivary alpha-amylase reactivity	$r = 0.46$	$P = 0.005$	– Correlational design does not allow for causal inferences to be made. – Small sample size limits generalizability. – Included both male and female participants and did not examine sex-specific effects. – Participants' scores on the measure of childhood adversity did not span the full range of possible values.

(continued)

Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Liu *et al.* (2015)	Case–Control Study	$n = 40$ reproductive-aged women (PMDD: $n = 20$)	PMDD diagnosis	Late luteal phase anterior cingulate cortex/medial prefrontal cortex GABA concentration	$d = -0.75$ (95% CI: −1.40, −0.11)	$P = 0.02$	– Limited statistical power due to small sample size. – Did not measure serum progesterone and estradiol to confirm that all participants were in the luteal phase.
				Late luteal phase left basal ganglia GABA concentration	$d = -0.82$ (95% CI: −1.48, −0.19)	$P = 0.01$	
Wittchen *et al.* (2003)	Prospective Cohort Study	$n = 1488$ women aged 14–24 years	PTSD diagnosis	PMDD diagnosis	OR = 11.7 (95% CI: 3.00, 46.2)	$P < 0.001$	– PMDD was assessed via retrospective self-report, which has been demonstrated to be less reliable than prospective self-report measures. – Restricted age range prevents generalizability of results to all reproductive-aged women. – Small number of cases ($n = 4$) met DSM-IV defined threshold for both PTSD and PMDD.
Girdler *et al.* (1998)	Case–Control Study	$n = 24$ reproductive-aged women (PMDD: $n = 12$)	History of sexual abuse		OR = 11 (95% CI: 1.06, 114.09)	$P = 0.02$	– Did not provide sufficient information to calculate effect size for five outcome variables. – Small sample size and convenience sampling limits generalizability. – Norepinephrine and cortisol measured only once at baseline.
			History of physical abuse	PMDD diagnosis	OR = 2.8 (95% CI: 0.53, 14.74)	$P = 0.22$	
Jacobs *et al.* (2015)	Prospective Cohort Study	$n = 742$ women aged 18–45 years	Number of adverse childhood exposures		RR = 1.09 (95% CI: 1.05, 1.13) RR = 1.07 (95% CI: 1.04, 1.10) FR = 0.97 (95% CI: 0.95, 0.99)		– Risk of self-report bias in all outcome measures. – Fertility difficulties based on self-report rather than formal clinical diagnosis. – Convenience sampling and demographic characteristics (i.e., primarily young African American women) limit generalizability.
			High exposure to adversity	Fertility difficulties Amenorrhea Fecundability	RR = 2.75 (95% CI: 1.45, 5.21) RR = 2.54 (95% CI: 1.52, 4.25) FR = 0.72 (95% CI: 0.52, 0.99)		
			Low exposure to adversity		RR = 1.51 (95% CI: 0.75, 3.05) RR = 1.90 (95% CI: 1.08, 3.33) FR = 0.81 (95% CI: 0.60, 1.08)		
Leblanc *et al.* (2020)	Cross-Sectional Ecologic Study	$n = 279$ women aged 19–64 years	Intimate partner violence		$b = -0.021$ (95% CI: −0.251, 0.210) $b = 1.255$ (95% CI: 0.852, 1.659) $b = 0.291$ (95% CI: 0.120, 0.561)	$P = 0.861$ $P < 0.001$ $P = 0.035$	– Study design precludes causal inferences. – Limited statistical power due to small sample size for large number of variables. – All variables measured via retrospective self-report and are thus subject to recall and misclassification biases.
			Childhood emotional abuse		$b = -0.046$ (95% CI: −0.154, 0.062) $b = 0.412$ (95% CI: 0.227, 0.598) $b = -0.011$ (95% CI: −0.136, 0.115)	$P = 0.401$ $P < 0.001$ $P = 0.866$	
			Childhood physical abuse	Lifetime STI Lifetime sex trading Concurrent partners	$b = 0.103$ (95% CI: −0.043, 0.249) $b = 0.019$ (95% CI: −0.203, 0.240) $b = 0.146$ (95% CI: −0.024, 0.316)	$P = 0.166$ $P = 0.870$ $P = 0.092$	
			Childhood sexual abuse		$b = 0.125$ (95% CI: 0.057, 0.193) $b = -0.060$ (95% CI: −0.170, 0.049) $b = 0.099$ (95% CI: 0.019, 0.180)	$P < 0.001$ $P = 0.281$ $P = 0.016$	
			Life stress		$b = 0.015$ (95% CI: −0.058, 0.088) $b = 0.192$ (95% CI: 0.095, 0.290) $b = -0.171$ (95% CI: −0.264, −0.079)	$P = 0.68$ $P < 0.001$ $P < 0.001$	

(continued)

Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Mota *et al.* (2019)	Cross-Sectional Study	$n = 36\,909$ US adults		Past-year STI	AOR = 1.54 (95% CI: 1.04, 2.28)	$P < 0.05$	– All outcome variables measured via retrospective self-report and are thus subject to recall and misclassification biases. – Reliability of exposure measure is suboptimal ($k = 0.34$–0.44). – Evaluated a limited number of all sexual risk outcomes.
			Lifetime PTSD diagnosis	Past-year sex with an injection drug user	AOR = 1.74 (95% CI: 1.15, 2.65)	$P < 0.01$	
				Never/almost never condom use in past year	AOR = 1.16 (95% CI: 0.91, 1.48)	$P > 0.05$	
Wamser-Nanney (2020)	Cross-Sectional Study	$n = 246$ trauma-exposed women aged 19–59 years	Trauma history		$b = -0.04$ (95% CI: −0.08, 0.009) OR = 1.01	$P = 0.1$ $P = 0.21$	– Study design precludes causal inferences. – All variables measured by retrospective self-report and are thus subject to recall and misclassification biases. – Generalizability limited by lack of ethnic diversity within the sample and use of convenience sampling.
			Posttraumatic stress	Time to conception	$b = 0.01$ (95% CI: 0.003, 0.02)	$P = 0.01$	
				Infertility	OR = 0.98	$P = 0.72$	
Lynch *et al.* (2014)	Prospective Cohort Study	$n = 501$ reproductive-aged couples	Highest salivary alpha-amylase tertile		FR = 0.71 (95% CI: 0.51, 1.00) RR = 2.07 (95% CI: 1.04, 4.11)	$P < 0.05$ $P > 0.05$	– Salivary biomarkers were based on only two samples despite participants being followed for up to 12 months. – Salivary samples collected at different points in participants' menstrual cycles. – Did not screen for pre-existing biological factors that may impair fertility (e.g., tubal occlusion). – Sample may have experienced less stress than is typical in pregnancy planners, limiting generalizability.
			Middle salivary alpha-amylase tertile		FR = 0.93 (95% CI: 0.68, 1.29) RR = 1.02 (95% CI: 0.48, 2.19)	$P > 0.05$	
			Highest salivary cortisol tertile	Fecundity	FR = 0.95 (95% CI: 0.69, 1.30)	$P > 0.05$	
				Infertility	RR = 0.84 (95% CI: 0.40, 1.76)		
			Middle salivary cortisol tertile		FR = 0.77 (95% CI: 0.56, 1.07) RR = 1.33 (95% CI: 0.69, 2.55)	$P > 0.05$	
Association between mental and reproductive health issues							
Ozkan *et al.* (2014)	Case–Control Study	$n = 120$ women aged 21–38 years (Infertile: $n = 80$)		IFNγ	RR = 0.12 (95% CI: 0.051, 0.325)	$P < 0.01$	– Studied only plasma cytokine levels, did not look at cytokine levels in endometrial tissue. – Blood was sampled only at one timepoint.
				IL17	RR = 2 (95% CI: 1.531, 2.661)	$P < 0.01$	
			Unexplained infertility diagnosis	TGFβ	RR = 1.9 (95% CI: 1.448, 2.518)	$P < 0.01$	
				IL6	RR = 1.7 (95% CI: 1.345, 2.324)	$P < 0.01$	
				TNFα	RR = 1.8 (95% CI: 1.406, 2.436)	$P < 0.01$	
				IL10	RR = 2 (95% CI: 1.548, 2.665)	$P < 0.01$	
				IL4	RR = 1.9 (95% CI: 1.513, 2.610)	$P < 0.01$	
Cohen *et al.* (2004)	Retrospective Cohort Study	$n = 198$ postpartum women	2+ maternal complications	Low vs. high posttraumatic stress postpartum	OR = 4.0 (95% CI: 1.3, 12.8)	$P = 0.005$	– Study design precludes causal inferences. – Lost 20.8% of original sample ($n = 253$) to follow-up. – Potentially underpowered due to low number of participants classified as having high posttraumatic stress ($n = 12$). – Did not assess posttraumatic or depressive symptoms prior to birth. – Excluded women who had premature or multiple births, who experienced pregnancy loss, or whose infants required intensive care, likely underestimating the experience of posttraumatic stress due to difficult birth. – Majority of sample was high income, limiting generalizability.
			Peripartum depression		OR = 18.9 (95% CI: 5.8, 62.4)	$P = 0.04$	
			2+ traumatic life events		OR = 3.2 (95% CI: 1.2, 8.3)	$P = 0.01$	

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Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Seng *et al.* (2010)	Cross-Sectional Study	$n = 3581$ reproductive-aged women (Pregnant sample: $n = 1581$)		Number of posttraumatic stress symptoms	$g = 0.24$ (95% CI: 0.17, 0.31)	$P < 0.001$	– Comparisons between pregnant and non-pregnant women made across studies with different protocols that were conducted 15 years apart.
			Sample (pregnant vs. general)	Current PTSD after sexual assault	RR = 3.38 (95% CI: 2.14, 5.35)	$P < 0.001$	– Did not consider pregnancy status of women in the general population sample. – Study design precludes causal inferences.
Demyttenaere *et al.* (1988)	Prospective Cohort Study	$n = 116$ reproductive aged women seeking AID	Trait anxiety	Duration of infertility	$r = 0.09$	$P = 0.27$	– Excluded women who were not in a stable relationship or had a current psychiatric disorder.
				AID cycle at which conception was achieved	$R^2 = 0.16$	$P < 0.001$	– Trait anxiety defined based on a single measurement. – Limited statistical power due to small sample size.
			Spontaneous abortion (Occurred vs. none)	Trait anxiety	$g = 0.76$ (95% CI: 0.10, 1.43)	$P < 0.02$	
Nillni *et al.* (2016)	Prospective Cohort Study	$n = 2146$ women trying to conceive	Baseline depressive symptoms (severe vs. none)		FR = 0.62 (95% CI: 0.43, 0.91)		– All variables were assessed using retrospective self-report measures, potentially introducing recall bias.
			10-unit increase in Major Depression Inventory score	Fecundability	FR = 0.90 (95% CI: 0.83, 0.97)		– Depressive symptoms were measured only at baseline. – Greater attrition among individuals with more severe depressive symptoms.
Shaw *et al.* (2014)	Retrospective Cohort Study	$n = 16\,334$ births among 14 047 women	Historical PTSD		AOR = 1.06 (95% CI: 0.84, 1.34)	$P = 0.6$	– Sample consisted of deliveries covered by the Veterans Health Administration and may not be generalizable to the general population.
			Past-year PTSD	Spontaneous preterm delivery	AOR = 1.35 (95% CI: 1.14, 1.61)	$P < 0.001$	– Did not account for age at which trauma occurred.
Meltzer-Brody *et al.* (2007)	Cross-Sectional Study	$n = 713$ women with chronic pelvic pain aged 18–66 years	Number of lifetime traumas		$\beta = -0.15$ $R^2 = 0.05$	$P < 0.001$	– Sampling method (convenience sample of patients referred to pelvic pain clinic) and demographic makeup (primarily white and highly educated) limits generalizability. – Retrospective self-report measures of exposure and outcome variables may be subject to recall bias.
			PTSD diagnosis	Healthy physical functioning	$\beta = 0.2$ $R^2 = 0.1$	$P < 0.001$	
				Number of nonpelvic medical symptoms	$\beta = 0.18$ $R^2 = 0.04$	$P < 0.001$	
				Number of lifetime surgeries	$\beta = -0.24$ $R^2 = 0.04$	$P < 0.001$	
					$\beta = 0.37$ $R^2 = 0.12$	$P < 0.001$	
					$\beta = 0.13$ $R^2 = 0.02$	$P < 0.001$	
Nillni *et al.* (2015)	Prospective Cohort Study	$n = 49$ trauma-exposed, reproductive-aged women (PTSD: $n = 22$)	Menstrual cycle phase (early follicular vs. midluteal)	Phobic anxiety severity	$d = 0.81$	$P = 0.009$	– Study may have been underpowered due to small sample. – Measure of PTSD asked participants to consider experience in the preceding 7 days, so ratings categorized as early follicular phase included the late-luteal phase. – Convenience sampling method and recruitment from Veterans' Affairs hospitals limits generalizability of sample.
				Overall symptom severity	$d = 0.63$	$P = 0.038$	
			Menstrual cycle phase×PTSD diagnosis		$d = 0.63$	$P = 0.034$	
					$d = 0.41$	$P > 0.05$	

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Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Farren *et al.* (2016)	Prospective Cohort Study	$n = 89$ reproductive aged-women (EPL: $n = 69$ Pregnant controls: $n = 20$)		Posttraumatic stress 1 month following (none/mild vs. moderate/severe)	OR = 8.24 (95% CI: 1.04, 65.37)	$P = 0.003$	– High attrition rate (39.4% of original 114 EPL and 60% of original 50 controls from recruitment to 1 month assessment). – Underpowered due to small sample size. – Outcome measures subject to self-report bias.
			Early pregnancy loss	Anxiety symptoms 1 month following (none/mild vs. moderate/severe)	OR = 4.21 (95% CI: 0.9, 19.77)	$P = 0.04$	
				Depressive symptoms 1 month following (none/mild vs. moderate/severe)	OR = 1.71 (95% CI: 0.35, 8.43)	$P > 0.05$	
Zuckerman *et al.* (2018)	Cross-Sectional Study	$n = 834$ reproductive-aged women (Dysmenorrhea: $n = 285$ NCPP: $n = 32$ Both: $n = 131$ Healthy controls: $n = 386$)	Comorbid dysmenorrhea and NCPP vs. Dysmenorrhea	Somatic symptoms	$g = 1.19$ (95% CI: 0.97, 1.42)	$P < 0.01$	– Small sample size of participants with non-cyclic pelvic pain alone. – All variables were based on self-reports rather than clinical interviews. – Study design precludes causal inferences.
				Anxiety symptoms	$g = 0.88$ (95% CI: 0.67, 1.1)	$P < 0.01$	
				Depressive symptoms	$g = 0.68$ (95% CI: 0.47, 0.89)	$P < 0.01$	
			Somatic symptoms	Pelvic pain	$\beta = 0.05$	$P < 0.001$	
			Dysmenorrhea	Anxiety symptoms	$g = 0.29$ (95% CI: 0.14, 0.44)	$P < 0.05$	
			NCPP		$g = 0.93$ (95% CI: 0.57, 1.30)	$P < 0.05$	
			Both		$g = 1.19$ (95% CI: 0.98, 1.40)	$P < 0.05$	
				Depressive symptoms	$g = 0.30$ (95% CI: 0.14, 0.45)	$P < 0.05$	
					$g = 0.70$ (95% CI: 0.34, 1.07)	$P < 0.05$	
					$g = 1.01$ (95% CI: 0.80, 1.22)	$P < 0.05$	
Creedy *et al.* (2000)	Prospective Cohort Study	$n = 499$ women in the last trimester of pregnancy	Level of obstetric intervention during childbirth	Acute trauma symptoms	$\beta = 0.351$	$P < 0.001$	– Provided insufficient information to calculate odds ratios (i.e., total proportion of women who reported stressful birth experiences). – Did not control for previous trauma history. – Outcome variables assessed retrospectively.
			Concern for baby's life		$\beta = 0.097$	$P = 0.03$	
			Dissatisfaction with intrapartum care		$\beta = -0.393$	$P < 0.001$	
Nillni *et al.* (2022)	Prospective Cohort Study	$n = 2643$ women aged 21–45 years	3–5 cycles to conceive	Postpartum depression	RR = 1.06 (95% CI: 0.77, 1.45)		– All variables measured via self-report, potentially introducing response bias. – Did not measure psychiatric symptoms or stressful life events.
			6–11 cycles to conceive		RR = 1.24 (95% CI: 0.90, 1.70)		
			12+ cycles to conceive		RR = 1.31 (95% CI: 0.87, 1.99)		
			Infertility × history of psychopathology		With history of psychopathology: RR = 1.55 (95% CI: 0.95, 2.53) Without history of psychopathology: RR = 0.76 (95% CI: 0.32, 1.84)		
			Infertility × perceived stress in early pregnancy		Early pregnancy perceived stress: $R^2 = 0.30$		
Association between trauma, mental and reproductive health, and menopause							
Choi *et al.* (2015)	Cross-Sectional Study	$n = 3176$ women aged 40–70 years in natural menopause	Daily life stress	Age at natural menopause	$\beta = -0.05$	$P = 0.023$	– Daily life stress operationalized by a single question at one timepoint. – Study design precludes causal inferences.

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Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Freeman *et al.* (2004)	Prospective Cohort Study	$n = 436$ women aged 35–47 years	Current MDD	Premenstrual Syndrome during 5-year study period	OR = 4.68 (95% CI: 3.44, 6.37)	$P < 0.001$	– Premenstrual Syndrome assessed by self-report and is thus potentially subject to misclassification bias.
			Premenstrual Syndrome at baseline	Hot flushes during perimenopause	OR = 2.09 (95% CI: 1.42, 3.08)	$P < 0.001$	
				Depressed mood during perimenopause	OR = 2.34 (95% CI: 1.60, 3.43)	$P < 0.001$	
				Decreased libido during perimenopause	OR = 1.54 (95% CI: 1.06, 2.24)	$P = 0.024$	
				Poor sleep during perimenopause	OR = 1.72 (95% CI: 1.16, 2.53)	$P = 0.007$	
Gibson *et al.* (2019)	Cross-Sectional Study	$n = 2016$ women aged 40–80 years	Lifetime emotional intimate partner violence	Difficulty sleeping	OR = 1.36 (95% CI: 1.09, 1.71)	$P = 0.001$	– Study design precludes causal inferences. – All variables measured via retrospective self-reports and may be subject to recall or self-report bias. – Did not consider age at which intimate partner violence or sexual assault occurred. – Difficulty sleeping and night sweats are symptoms of both posttraumatic stress disorder and menopause.
				Night sweats	OR = 1.50 (95% CI: 1.19, 1.89)	$P < 0.001$	
				Pain with intercourse	OR = 1.60 (95% CI: 1.14, 2.25)	$P = 0.008$	
			Lifetime physical intimate partner violence	Night sweats	OR = 1.33 (95% CI: 1.03, 1.72)	$P = 0.02$	
			Lifetime sexual assault	Vaginal dryness	OR = 1.41 (95% CI: 1.10, 1.82)	$P = 0.005$	
				Vaginal irritation	OR = 1.42 (95% CI: 1.04, 1.95)	$P = 0.02$	
				Pain with intercourse	OR = 1.44 (95% CI: 1.00, 2.06)	$P = 0.02$	
			Current posttraumatic stress	Difficulty sleeping	OR = 3.02 (95% CI: 2.22, 4.09)	$P < 0.01$	
				Hot flashes	OR = 1.69 (95% CI: 1.34, 2.12)	$P < 0.01$	
				Night sweats	OR = 1.72 (95% CI: 1.37, 2.15)	$P < 0.01$	
				Vaginal dryness	OR = 1.73 (95% CI: 1.37, 2.18)	$P < 0.01$	
				Vaginal irritation	OR = 2.20 (95% CI: 1.66, 2.93)	$P < 0.01$	
				Pain with intercourse	OR = 2.16 (95% CI: 1.57, 2.98)	$P < 0.01$	
Harlow *et al.* (2003)	Prospective Cohort Study	$n = 976$ premenopausal women aged 36–45 years ($n = 332$ with depression history $n = 644$ without depression history)		Perimenopause rate over 36 months	HR = 1.2 (95% CI: 0.9, 1.6)		– Variables operationalized by retrospective self-report and is potentially subject to recall bias. – Since potential participations were excluded if they had already begun perimenopause, older participants (ages 41–45 years) may not be representative of all women in that age group.
			Baseline depression score (High vs. low)	Depression history (with vs. without)	HR = 2.0 (95% CI: 1.3, 3.0)		
Nelson *et al.* (2011)	Prospective Cohort Study	$n = 291$ premenopausal women aged 35–47 years		Decreased libido	OR = 1.86 (95% CI: 1.05, 3.31)		– Small sample size limits generalizability. – Infertility and decreased libido were operationalized question each. – All variables captured by retrospective self-report measures.
			Infertility	Vaginal dryness	OR = 2.79 (95% CI: 1.19, 6.94)		
Pal *et al.* (2010)	Cross-Sectional Study	$n = 89$ infertile women under 42 years of age	History of recreational substance use	Diminished ovarian reserve	OR = 3.71 (95% CI: 1.19, 11.49)	$P = 0.023$	– Study design precludes causal inferences. – Potentially underpowered due to small sample size. – Findings cannot be generalized to women who have not been diagnosed with infertility. – Exposure variables measured via retrospective self-report and are potentially subject to recall and misclassification biases.
			Chronic psychosocial stress		OR = 3.25 (95% CI: 1.16, 9.11)	$P = 0.025$	
			History of abuse		OR = 2.2 (95% CI: 0.51, 9.81)	$P = 0.276$	

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Table 1. (continued)

Paper	Study design	Sample size	Exposure variable(s)	Outcome variable(s)	Effect size	P-value	Limitations
Association between mental health, age at menopause, and cognitive decline							
Aggarwal *et al.* (2014)	Prospective Cohort Study	$n = 6207$ men and women aged 65 years or older	Perceived stress	Initial cognitive scores	$b = -0.0379$ (SE = 0.0025)	$P < 0.001$	– Measure of perceived stress was shortened to only six items and had a borderline-acceptable reliability coefficient ($\alpha = 0.75$)
				Rate of cognitive decline	$b = -0.0015$ (SE = 0.0004)	$P < 0.001$	– Measure of perceived stress did not consider source of stressors or how long participants had experienced that level of stress between timepoints.
Brenowitz *et al.* (2021)	Prospective Cohort Study	$n = 6122$ men and women aged 20–89 years	Depressive symptoms in early adulthood		OR = 1.59 (95% CI: 1.35, 1.87) $\beta = -0.07$ (95% CI: −0.13, −0.01)		– Depressive symptom trajectories for older adults were estimated based on data from young adults, leading to underestimation of depressive symptoms in early adulthood that may have resulted in misclassification bias.
			Depressive symptoms in mid-life	Cognitive impairment Cognitive decline over 10 years	OR = 1.94 (95% CI: 1.16, 3.26) $\beta = -0.07$ (95% CI: −0.29, 0.16)		
			Depressive symptoms in late adulthood		OR = 1.77 (95% CI: 1.42, 2.21) $\beta = -0.26$ (95% CI: −0.33, −0.20)		– Definition of cognitive impairment included both those with substantial impairment on cognitive battery and diagnosis of dementia.
Ryan *et al.* (2014)	Prospective Cohort Study	$n = 4868$ women aged 65 years or older	Menopause before age 40 years	Impaired verbal fluency Impaired verbal memory Impaired psychomotor speed Impaired executive function Impaired global function 7-year decline in verbal fluency 7-year decline in verbal memory 7-year decline in psychomotor speed 7-year decline in executive function 7-year decline in global function Risk of dementia	OR = 2.24 (95% CI: 1.44, 3.48) OR = 1.77 (95% CI: 1.16, 2.72) OR = 1.13 (95% CI: 0.71, 1.79) OR = 1.02 (95% CI: 0.62, 1.69) OR = 1.44 (95% CI: 0.88, 2.37) HR = 1.05 (95% CI: 0.80, 1.36) HR = 1.10 (95% CI: 0.85, 1.45) HR = 1.36 (95% CI: 1.09, 1.71) HR = 1.10 (95% CI: 0.82, 1.47) HR = 1.35 (95% CI: 1.05, 1.74) HR = 1.23 (95% CI: 0.76, 2.00)	$P < 0.001$ $P < 0.001$ $P = 0.62$ $P = 0.93$ $P = 0.15$ $P = 0.74$ $P = 0.45$ $P = 0.01$ $P = 0.54$ $P = 0.02$ $P = 0.40$	– Included women with both surgical and natural menopause. – Limited sample size of women with menopause before 40 ($n = 226$) and natural menopause before 40 ($n = 100$), thus potentially lacking statistical power to detect small to medium-sized effects. – Excluded participants included a higher proportion of women with poor cognitive function and early menopause than the analyzed sample. – Did not control for childhood cognition, which has been associated with later age at menopause.
Thurston *et al.* (2022)	Cross-Sectional Study	$n = 145$ women aged 45–67 years	Trauma exposure	Volume of white matter hyperintensities	$b = 0.24$ (SE = 0.09)	$P < 0.01$	– Study design precludes causal inferences. – Did not assess age at which trauma occurred nor its chronicity.
Wilson *et al.* (2007)	Prospective Cohort Study	$n = 219$ Catholic clergy members		Dementia proximate to death	OR = 1.71 (95% CI: 1.20, 2.44)		– Due to the small sample size and nature of the sample (Catholic clergy members) result may not be generalizable to the general population. – Brain pathology can contribute to psychological distress, confounding the relationships drawn in this study.
			Chronic distress	Global cognitive score proximate to death	$b = -0.236$ (SE = 0.066)	$P < 0.001$	

PMDD, premenstrual dysphoric disorder; PTSD, posttraumatic stress disorder; GABA, gamma-aminobutyric acid; DSM-IV, Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; TNFα, tumor necrosis factor alpha; IL10, interleukin 10; IFNγ, interferon gamma; IL6, interleukin 6; IL4, interleukin 4; IL35, interleukin 35; IL17, interleukin 17; AID, artificial donor insemination; EPL, early pregnancy loss; NCPP, noncyclic pelvic pain; MDD, major depressive disorder; OR, odds ration; 95% CI, 95% confidence interval; HR, hazard ratio; *b*, unstandardized regression coefficient; *r*, Pearson correlation coefficient; *d*, Cohen's *d*; RR, relative risk ratio; FR, fecundability ratio; AOR, adjusted odds ratio; β, standardized regression coefficient; *g*, Hedges' *g*; R^2, coefficient of determination.

inflammatory cytokines released in response to stress block glutamatergic (GLU) reuptake and increase GLU release at astrocytes, and also activate indoleamine 2,3-dioxygenase so that tryptophan is converted into kynurenine instead of serotonin. Consequently, kynurenine is converted into quinolinic acid, which increases the GLU tone by activating N-methyl-D-aspartate (NMDA) receptors and blocking GLU reuptake. The overall increase in GLU synaptic availability results in increased excitotoxicity and decreased production of BDNF.

Reductions in BDNF have previously been linked to reductions in GABAergic tone and receptor expression; thus, its decrease may result in hypoactivity of the GABAergic system and, consequently, hypoactivity of the HPA axis in response to stress (Zhu *et al.*, 2019). This reduction in GABAergic activity may then be maintained by the loss of inflammatory inhibition, associated with reduced levels of cortisol and exacerbated in the luteal phase of the menstrual cycle by the sudden drop in progesterone levels, which has anti-inflammatory effects (O'Brien *et al.*, 2007; Liu *et al.*, 2017). While a manual preliminary review of the literature found few studies that refute these hypotheses, higher cortisol levels have been observed among women with PMS (a less severe form of PMDD) and potential variability in this proposed mechanism should be recognized (Rasgon *et al.*, 2000). More so, there is evidence that GABA levels may increase between the follicular and luteal phases in women with PMDD (Gingnell *et al.*, 2014), countering the proposed suppression of the GABAergic system and further highlighting potential differences in brain function among women with PMDD. Considering this evidence, while there appears to be more research supporting a decrease in GABA levels between the follicular and luteal phases (Halbreich *et al.*, 1996; Liu *et al.*, 2015), the involvement of the GABAergic system in PMDD is consistently reported (Sundström Poromaa *et al.*, 2003).

Furthermore, since cortisol has been shown to inhibit the release of norepinephrine, the HPA axis hypoactivity may contribute to the aforementioned hyperactivity of the SNS (Fries *et al.*, 2005). It may be, then, that reproductive dysfunction, including PMDD, manifests as an indicator of the HPA axis and SNS dysfunction caused by increased inflammation and thus acts as a marker for increased risk of future reproductive health problems (e.g., endometriosis, fibroids, polycystic ovaries, and potential future infertility; Duleba and Dokras, 2012; Ozkan *et al.*, 2014; Liang *et al.*, 2015; Wu *et al.*, 2015; Orciani *et al.*, 2018).

These neuroendocrine mechanisms demonstrate the plausibility of an intimate connection between stress and reproductive physiology that may carry severe implications for a woman's health across decades of life. The potential associations between stress-induced alterations of biological mechanisms and reproductive and birth outcomes warrant further exploration to investigate the hypothesis that trauma may generally affect a woman's experience of reproductive health and commonly increase her risk of developing reproductive disorders. In conclusion, this area of inquiry remains in its infancy and inconsistent findings are reported; further research is necessary to confirm and elucidate the role of SNS hyperactivity, HPA–HPG axis connectivity, GABAergic transmission and inflammation, in the relation between trauma and female reproductive disorders such as PMDD, endometriosis, infertility, pregnancy loss, and early menopause.

Conclusion

Female reproductive disorders constitute a substantial and prevalent burden on women's lives, yet many conditions remain underacknowledged and under-researched. Recent evidence that traumatic experiences convey an increased risk of these disorders underscores a need for more attention afforded to the role of traumatic exposures in female reproductive health across the reproductive lifecourse. In this paper, we proposed a hypothetical framework linking trauma to increased risk of mental and reproductive health issues, which contributes to increased risk for premature menopause and more severe menopausal symptoms, and, as a result, an increased risk for faster and more severe cognitive decline in late life. Within this framework we proposed a cyclical relationship between mental and reproductive health problems wherein adverse outcomes in one dimension increase the risk of developing health concerns in the other, including infertility and pregnancy loss. We have also noted the potential for racial trauma to instigate such a cycle, potentially contributing to racial disparities in adverse reproductive outcomes. Finally, in investigating the biological plausibility of this framework, we proposed two core pathways through which trauma might alter neuroendocrinological processes to increase the risk of adverse mental and reproductive outcomes: hypoactivation of the HPA-axis via inflammation-induced suppression of GABAergic transmission, and hyperactivation of the SNS due to a decrease in cortisol and a consequent reduction in norepinephrine inhibition.

In sum, we suggest that a cyclical interaction between mental and reproductive health allows for the deleterious effects of trauma to compound across the lifecourse and necessitates early intervention to prevent the development of further reproductive health problems. We highlight the importance of considering psychosocial factors in the aetiology of female reproductive health disorders and offer the proposed framework as a set of preliminary hypotheses to guide a research agenda seeking to uncover the environmental and biological mechanisms that contribute to the development and maintenance of adverse female reproductive outcomes. It is critical to note that the pathways proposed herein are highly complex and, should they exist, will certainly involve mechanisms and influences that are beyond the scope of the broad overview covered here, but they must be considered in testing individual associations. Future systematic investigations are critical to test the individual hypotheses presented in this article and inform the development of more effective prevention and intervention methods to relieve the physical and psychological burden that reproductive health disorders can impose throughout women's lives.

Authors' roles

A.H., J.P., and C.M. devised the project, and developed the conceptual ideas and theoretical frameworks. J.P. and A.H. conducted the literature review, drafted the manuscript, and prepared figures and tables. L.M., Y.Z., G.R., H.T., N.T., V.M., C.D.A., and C.M. interpreted the manuscript and critically revised it for intellectual content. C.M. and C.D.A. provided leadership and oversight of the project and supervised the work. All authors approved the final version.

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Conflict of interest

No conflicts of interest to disclose.

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