Women's reproductive mental health: currently available evidence and future directions for research, clinical practice and health policy

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Sex and gender differences in the epidemiology of mental disorders are well documented. Less well understood are the drivers of these differences. Reproductive health represents one of the gendered determinants of mental health that may affect women throughout their life course. In this paper, we review common reproductive events that may be associated with mental ill health, including menstruation (with premenstrual dysphoric disorder appearing for the first time in recent classifications of mental disorders), contraception, abortion, sexual dysfunction, hypersexuality, sexual violence, reproductive coercion, infertility and associated gynaecological conditions, and menopause. Such reproductive events may differentially affect women globally via a range of potential biological and psychosocial mechanisms. These include, for example, vulnerability to the physiological changes in hormone levels across the menstrual cycle; side effects of treatment of mental disorders; inflammation underpinning endometriosis and polycystic ovarian syndrome as well as mental disorders such as depression; intersections with gender disadvantage manifesting, for example, as structural barriers in accessing menstrual products and sanitation, contraception and abortion, underscoring the broader social determinants impacting women's mental health. Greater understanding of these mechanisms is guiding the development of effective interventions, which are also reviewed here. However, key evidence gaps remain, partly as a result of the historic gender bias in mental health research, and the neglect of reproductive health in clinical practice. Furthermore, while several women's health strategies have recently been proposed internationally, they do not usually include a focus on mental health across the life course, particularly for women with severe mental illness. Integrating co-designed reproductive health interventions into primary and secondary mental health care settings, providing tailored care, increasing the evidence base on effective interventions, and empowering women to make informed choices about their reproductive health, could improve not only reproductive health but also women's mental health across the life course.

Key words: Reproductive mental health, menstruation, contraception, abortion, sexual violence, reproductive coercion, sexual dysfunction, compulsive sexual behaviour disorder, infertility, menopause

It is well established that there are sex and gender differences in the prevalence, risk factors and natural history of mental disorders[1]. For example, studies show that the lifetime prevalence of mood and anxiety disorders in women is twice that of men[2,3]. The research evidence is robust, such that these are likely to represent true differences (as opposed to "apparent" differences due to any biases)[1].

The impact of reproductive health on mental health is lifelong and not restricted to childbearing years, and is linked to human rights. Thus, reproductive health represents one of the gendered determinants of mental health impacting women throughout their life course. In recent decades, there have been improvements in public awareness of women's reproductive rights – concepts of "period poverty" (i.e., systemic inequalities in access to menstrual products and education) and sexual abuse, for example, are no longer as taboo as they were in the last century – but stigma around discussion of reproductive health is still common globally. In part related to this, the interface between women's reproductive and mental health across the life course continues to be overlooked by researchers, clinicians and policy makers, despite its centrality in women's lives.

Although several women's health strategies have recently been put forward internationally[4-6], they usually do not include a focus on mental health across the life course. They also fail to address the needs of women with severe mental illness, who are particularly likely to face significant reproductive health inequalities.

Specific mechanisms for the relationship between mental health and reproductive events may involve complex biological, psychological and/or social pathways, which are discussed, where there is evidence, in the specific sections of this paper. These may include shared genetic and environmental (e.g., poverty, social discrimination) factors.

It is well established that sex hormones play a crucial role in brain development and functioning[7], with significant implications for women's mental health[1]. Understanding the neuroendocrine mechanisms underlying women's mental health could uncover valuable new insights into how to optimize exogenous hormonal and non-hormonal treatments for women's mental disorders.

The social determinants of mental disorders are unequally distributed[8]. Gender roles are socialized from an early age, and traditional gender roles are often associated with stigma around discussion of reproductive health, limited education for girls and women, and differential exposure of women to a range of social stressors in the home and workplace[3], including gender harassment and discrimination[1]. Women often perform multiple roles, including caring roles, which are a frequent source of distress. They are also more likely to experience intimate partner violence and sexual abuse, which are known risk factors for mental disorder[9].

Like the risk factors (for mental disorders) that are specific to women, many of the

reproduction-related topics considered here have been neglected in mental health research[10,11]. While clinicians fail to routinely ask about sexual functioning and reproductive events, women are unlikely to share information on sexual dysfunction, hypersexuality, or menstrual worsening of depressive or psychotic symptoms, with opportunities thus missed to address such problems with, for example, changes in psychotropic medication. In societies with high levels of gender disadvantage, it is particularly difficult for women to be empowered to speak of their reproductive needs.

Inequities in access to contraception and reproductive coercion experienced by women with mental illness result in increased rates of unwanted pregnancy and abortion. If co-designed reproductive health interventions were integrated into primary and secondary mental health care settings globally, women with mental disorder would be more likely to make informed choices about their reproductive health, which would potentially improve not only their reproductive health but also their mental health.

We hope that this paper and the accompanying commentaries will advance the understanding and treatment of mental health problems in the context of women's reproductive health across the life course. We do not include here events related to pregnancy and the postpartum, as these have been covered recently in another Forum published in this journal[12].

MENSTRUATION AND MENSTRUAL-RELATED DISORDERS

Menstruation refers to the cyclic physiological process in which the endometrium of the uterus sheds through vaginal bleeding, occurring in females of reproductive age as part of the menstrual cycle. This is primarily regulated by fluctuations in levels of oestrogen and progesterone, orchestrated by the hypothalamic-pituitary-ovarian axis.

The cycle can be divided into several phases: the follicular phase, characterized by the development of ovarian follicles and rising levels of follicle stimulating hormone (FSH) and oestradiol; ovulation, triggered by a surge in luteinizing hormone (LH) and involving the release of a mature egg from the ovary; and the luteal phase, marked by the secretion of progesterone and oestradiol from the corpus luteum, which develops from the remnant of the follicle, to prepare the uterus for potential implantation. If fertilization does not occur, hormone levels decline, leading to the shedding of the endometrial lining during menstruation, marking the beginning of a new cycle[13].

The periodic changes that characterize the menstrual cycle are associated with an increased risk for a range of mental health conditions and psychiatric outcomes.

Premenstrual syndrome (PMS) is the most common menstrual disorder, encompassing a

range of physical and psychological symptoms occurring in the luteal phase of the menstrual cycle. PMS is estimated to be clinically significant in 20-30% of women[14]. Psychological manifestations may include anxiety, depression, irritability, restlessness, insomnia or excessive sleepiness, and feeling that everything is an effort[15]. However, challenges exist in accurately measuring PMS, due to variability in the type, severity and timing of symptoms across individuals and menstrual cycles; the reliance on self-reported symptoms, which can be influenced by individual perceptions and interpretations as well as by recall bias; the overlap between symptoms of PMS and those of other health conditions, including mood disorders; and a lack of objective diagnostic criteria. Indeed, a systematic review of prospective studies found no convincing evidence for the existence of a distinct premenstrual negative mood syndrome in the general population, and noted that synthesis of study findings was hindered by the diversity of sampling methods, assessment instruments, and cycle phase definitions used in the contributing studies[16].

A minority of women will experience a more severe form of mood disturbance, premenstrual dysphoric disorder (PMDD), which has been included for the first time in the ICD-11[17] and DSM-5[18] classifications. This diagnosis requires that, in the majority of menstrual cycles, at least five symptoms are present in the week before the onset of menstruation, which start to improve within a few days after that onset, and become minimal or absent in the week after menstruation. These must include one or more affective symptoms (marked affective lability, irritability or anger, depressed mood, or anxiety) and one or more additional symptoms (decreased interest in usual activities, concentration difficulties, marked lack of energy, marked change in appetite, hypersomnia or insomnia, a sense of being overwhelmed or out of control, and physical symptoms such as breast tenderness or swelling, joint or muscle pain, and a sensation of “bloating”). The symptoms should be associated with significant distress or interference with social functioning.

When adhering strictly to diagnostic criteria, which requires prospective tracking of symptoms over two cycles, the point prevalence of PMDD is 1.6% of menstruating females[19]. In studies using retrospective reporting of symptoms, this rises to 7.7%[19]. The condition is associated with an increased risk of suicidal ideation[20], and has a similar impact on quality of life as other chronic health problems[21].

The mechanisms underlying PMDD have been examined through experimental manipulation of hormones[22,23]. In women with the disorder, complete suppression of oestradiol and progesterone is sufficient to control symptoms, while the add back of either hormone reproduces the symptoms[24]. Interestingly, high steady levels of these hormones are also sufficient to control symptoms[25]. This has led to a model in which PMDD is caused by vulnerability to the physiological changes in hormone levels across the menstrual cycle[26].

There are various treatments for PMDD. Selective serotonin reuptake inhibitors (SSRIs)

are recommended as a first-line treatment by UK[27] and American[28] guidelines. These medications have been shown to be effective in meta-analyses of randomized controlled trials (RCTs), with a larger effect size than in depression (a standardized mean difference of 0.65)[29]. They are as effective when dosed intermittently (during the luteal phase of the cycle) as when they are used continuously throughout the cycle[30], and have a peak effect at 48 hours[31], suggesting a different mechanism of action than in depression.

Another treatment strategy is to stabilize hormone fluctuations, either through exogenous hormones or by suppression of the cycle using gonadotropin releasing hormone (GnRH) analogues. This is initially recommended in the form of combined oral contraceptives[27,28]. A network meta-analysis has shown that this treatment is effective compared with placebo[32], with no one formulation superior to others. Notably, while these interventions were effective in reducing premenstrual symptoms, reduction in depressive symptoms specifically did not reach statistical significance. Another method is using transdermal oestradiol; although this is recommended by UK guidelines[27], it is based on lower-quality evidence[33] and, notably, it is not recommended by American guidelines[28].

A range of mental disorders have evidence of menstrual exacerbation. Systematic reviews have identified some evidence of menstrual worsening in depression, mania, panic disorder, eating disorders, and emotionally unstable personality disorder[34,35]. In a meta-analysis, the perimenstrual phase was associated with an increased risk of psychosis, with an admission rate 1.5 times higher than baseline[36]. However, firm conclusions are limited by methodological problems. Most studies compared symptom ratings at one or two timepoints in the cycle. This is inadequate, as menstrual cycles show marked variability within and between individuals. Symptom changes should ideally be studied using a within-person design, over multiple timepoints, with robust measurement of cycle phase. Prospective rating of symptoms is needed, as retrospective recall is prone to bias.

While guidelines from the Royal College of Obstetricians and Gynaecologists advocate the option of hormonal treatments for mental disorders exacerbated by the menstrual cycle, this is based on limited evidence[27]. Further research into the impact of the menstrual cycle in mental disorders and the effects of hormone-based treatments is needed. It is nonetheless important that health care professionals working with menstruating women enquire as to whether their menstrual cycle is associated with changes in their mental health.

Irrespective of psychiatric diagnosis, the menstrual cycle appears to confer particular risk for suicidal behaviour. In women with a history of suicidality, the time around menstruation is associated with increased suicidal ideation and planning[37]. Depressive symptoms appear to be the main mediators of this perimenstrual exacerbation[37]. Although a meta-analysis reported that suicidal ideation was unrelated to the stage of menstrual cycle, it found evidence for a 17% greater risk of suicide attempts, 26% greater risk of suicide deaths, and 20% greater risk

of psychiatric admission at menstruation, with the menstrual phase more strongly associated with serious mental health outcomes than the premenstrual phase[38]. While completed suicide is more common in men, suicide attempts are more frequent in women[39], and menstrual cycle fluctuations are a potentially modifiable risk factor for suicidality in women.

Although hormonal fluctuations appear to drive the above findings, social factors can profoundly shape women's experiences of menstruation and their mental well-being. Menstruation continues to be stigmatized in societies around the world[40]. Such stigma may prevent women from accessing health care for menstrual problems, as well as being a contributing factor to mental disorders. Sociological studies illustrate how women often conceal menstrual symptoms due to entrenched social expectations, which influences daily activities, dress choices and interpersonal communication[41].

Feminist social scientists have also highlighted how menstruation is embedded within broader socio-cultural contexts, affecting women's gender identity, body image, and social status[42]. Cultural beliefs and media contribute to this broader social context, with profound consequences for women's psychological and sexual well-being[42]. Moreover, so-called "period poverty" – a global health concern estimated to affect up to 15% of young women in even urban high-income settings[43] – highlights systemic inequalities in access to menstrual products, education and sanitation, underscoring the broader social determinants impacting women's mental health.

CONTRACEPTION

The term contraception encompasses all methods to prevent pregnancy. It has been described as one of the most cost-effective health care interventions, in terms of preventing unintended pregnancy (defined as a pregnancy that occurs earlier than desired or is not wanted at all[44]) and reducing maternal and neonatal mortality[45]. Avoiding unintended pregnancy enhances educational opportunities for girls, with far-reaching consequences for life outcomes. Nevertheless, contraception has a complex relationship with mental health and, despite its use by a substantial proportion of the world's population, rigorous investigation of this relationship has been relatively recent[46].

Forms of barrier contraception have been used since antiquity. Modern barrier methods, such as the male condom, offer the advantage of protecting against sexually transmitted infections, in addition to pregnancy[47]. In typical use, barrier methods are less effective in preventing pregnancy than hormonal contraceptives, and generally require the cooperation of both partners[47]. The advent of hormonal contraception has afforded women's reproductive freedom, aided effective family planning, and provided symptom relief for conditions such as

acne, endometriosis and the aforementioned PMDD[48]. In 2022, it was estimated that modern contraception prevented approximately 29 million unsafe abortions and 148,000 maternal deaths in lower-income countries in a single year[49].

Although in low- and middle-income countries there has been a clear rise in modern contraceptive use over the past decade, the overall percentage use remains lower than in high-income countries. Shorter-acting forms of hormonal contraception are more common in low- than in high-income countries, while longer-acting formulations are more frequently used in the latter[50]. The most common hormonal method globally is the oral contraceptive with formulations of either combined oestrogen and progestin or progestin-only[51]. Non-oral forms can also be combined (e.g., patches or vaginal rings) or progestin-only (e.g., injections, implants or the levonorgestrel-releasing intrauterine system). Combined contraceptives exert action primarily through the inhibition of ovulation, while progestin-only contraceptives act to thicken cervical mucus and thin the uterine endometrium[52].

There is most likely a bidirectional relationship between women's mental health and the choice of contraceptive method, the way in which it is used, and its subsequent effectiveness. Hormonal contraception decreases the use of barrier contraception, with a consequent increased risk of sexually transmitted infections[53]. Contraception effectiveness is known to be affected by a range of factors, including adherence, and there is evidence for reduced adherence in women with mental disorders. In severe mental illness such as schizophrenia[54], symptoms such as impaired cognitive function, disorganization and impulsivity may compromise consistent or correct use of contraceptives[55]. There may also be a relationship between depression and not using contraception, contraceptive discontinuation, or inconsistent contraceptive use.

In a cohort of 52,325 women in the US, those with a history of depression in the year prior to contraception initiation were more likely to use it inconsistently, discontinue it, or switch to another form within a year of initiation. In the same study, women with depression were also less likely to use the oral contraceptive pill, favouring other forms of hormonal contraception (e.g., patches or rings)[56]. The wider body of evidence yields mixed findings as to whether longer- or shorter-acting forms of contraception are preferred among women with depression[57-60]. However, evidence from prospective studies confirms a relationship between depression and subsequent poorer contraceptive adherence[57,58,61,62].

While there are clear benefits to women's mental health from having access to contraception, there is mixed evidence of the impact of hormonal contraception on mental health. Some observational studies have suggested an association between the use of this contraception and an increased risk of subsequent depression. In a Danish national cohort, the risk of a first diagnosis of depression or antidepressant use increased among those using any form of hormonal contraception, compared to those who did not[63]. While these

associations could reflect reverse causality, subsequent studies have suggested that the risk for depression is most pronounced with progestin-only forms of hormonal contraception[64].

A UK Biobank study attempted to overcome the issue of reverse causality using sister pairings[65]. Compared to those who had never used contraception, oral contraceptive users displayed an increased risk of depression, predominantly within the first two years of initiation (hazard ratio, HR=1.71; 95% CI: 1.55-1.88), and the sibling analysis suggested a causative effect. However, two RCTs (N=348 and N=202) of combined oral contraceptive versus placebo found no associated increase in depressive symptoms, although there was some association with anxiety symptoms[66] and a decline in general well-being[67].

A recent systematic review and meta-analysis concluded that oral contraceptives are not associated with the development of mental health symptoms in the general population, though noting that adolescents and users of progestin-only preparations are potentially at increased risk[64]. Most studies included in the review focused exclusively on depressive rather than anxiety symptoms, and the majority were observational. Another systematic review found a lack of evidence of a relationship between progestin-only contraceptives and depression, though there was a dearth of high-quality studies[68].

Another mental health outcome which has been investigated in relation to contraception use is suicidal behaviour, including suicidal ideation, suicide attempts and completed suicide. Three large database studies reported an association between suicidal behaviour and oral contraceptive use, particularly within one year of treatment initiation[69-71]. However, a systematic review found that the relationship between hormonal contraceptive use and suicide risk displays considerable variability across studies[72]. Of nine studies reporting on six samples (N=683,198), some suggested no association or even a protective effect against suicide attempts and completed suicide, while others indicated an increased risk of suicide attempts and completed suicide. Inconsistencies in results were attributed to various factors, including variability in samples and consideration of concurrent depressive symptoms. None of the included studies adjusted for family mental health history or childhood adversity as potential confounders. Although the review was unable to draw a firm conclusion regarding an association between hormonal contraceptive use and attempted or completed suicide, it reported some evidence suggesting a higher risk of attempted suicide at initiation of hormonal contraceptive use compared to continued use and that, as such, adolescent women experienced the highest risk. Further research using population-based samples and including exposure to more recent hormonal contraceptive methods is needed to clarify this relationship.

High discontinuation rates have complicated analyses in this field. Many studies have found short-term associations between worsening mental health and hormonal contraception[63,69-71], suggesting that longer duration of use is protective. However, these results could indicate healthy survivor bias, particularly in population-based studies. This is

because users experiencing adverse symptoms are more likely to discontinue treatment early, so that the remaining participants will present with more tolerable side effects.

There are benefits and potential risks of contraception to women's mental health, and each individual has the right to make choices over her reproductive health. When considering the mental health risks associated with use of hormonal contraception, there is suggestive evidence that younger women, those with a history of depression, and those using progestin-only preparations are at highest risk. While more definitive research is awaited, an individualized approach to contraceptive decision making is likely to yield the best outcomes for women and their mental health, including the avoidance of unintended pregnancy.

ABORTION

Induced abortion, also known as termination of pregnancy, is a medical procedure to end pregnancy, which can be done using medication or through surgical intervention. We focus here on induced abortion and do not cover spontaneous abortion, commonly referred to as miscarriage or early pregnancy loss.

Global trends show a decline in rates of unintended pregnancy[72,73], partly due to improved access to contraception. However, existing contraceptive methods have limitations, and some women who are unable or unwilling to use them may still wish to avoid pregnancy. Additionally, circumstances may make continuing a (planned) pregnancy challenging for some women. Ensuring access to safe and legal abortion, alongside effective contraception, is therefore essential to promoting reproductive autonomy.

One study[74] reported a reduction of abortion rates in Europe and North America between 1990-1994 and 2010-2014, with rates stabilizing elsewhere, regardless of the status of legal abortion[74]. Although another study[75] similarly estimated a reduction of the global abortion rate for approximately 15 years after 1990-1994, it also found that, by 2015-2019, the abortion rate returned similar to that estimated for 1990-1994. Worldwide, in 2015-2019, there were an estimated 121 million unintended pregnancies annually, corresponding to a global rate of 64 per 1,000 women aged 15-49 years. Of these pregnancies, approximately 61% ended in abortion, with a global abortion rate of 39 per 1,000 women aged 15-49 years. Disparities in abortion rates were observed across World Bank income groups, with middle-income countries exhibiting the highest rate (44 abortions per 1,000 women aged 15-49 years) and high-income countries the lowest (15 abortions per 1,000 women aged 15-49 years)[75].

Within each World Bank income group, countries with more restrictive abortion laws reported higher rates of unintended pregnancies compared to those with broader legal access to abortion services. Specifically, high-income countries where abortion is broadly legal

exhibited the lowest annual average rate of unintended pregnancies (30 per 1,000 women aged 15-49 years), whereas low-income countries with restrictive abortion laws experienced the highest rate (101 pregnancies per 1,000 women aged 15-49 years). Furthermore, the annual abortion rate varied substantially across income groups and legal frameworks. In high-income countries where abortion was broadly legal, the abortion rate stood at 11 per 1,000 women aged 15-49 years, notably lower than in high-income countries with restrictive laws and middle- and low-income countries regardless of legal status.

Several rigorous studies[76-78] and reviews of the literature[79-85] have consistently concluded that abortion does not increase the risk of mental disorders. For example, in a population-based cohort study utilizing Danish population registry data, researchers compared the psychiatric outcomes of girls and women who underwent first-trimester induced abortion or childbirth between 1995 and 2007, finding that the incidence of psychiatric contact did not significantly increase after abortion (14.6 to 15.2 per 1,000 person years)[83].

Other mental health outcomes have also been used in Danish registries. When first-time antidepressant prescriptions were considered, there was no evidence of an increase in prescriptions during the year following (incidence rate ratio, IRR=1.54; 95% CI: 1.45-1.62) compared to the year prior to abortion (IRR=1.46; 95% CI: 1.38-1.54) (compared to those not undergoing abortion)[86]. Another outcome used has been first-time non-fatal suicide attempts: there was no evidence of an increase between the year prior to (IRR=2.46; 95% CI: 2.22-2.72) and the year after an abortion (IRR=2.54; 95% CI: 2.29-2.81)[87]. A Dutch prospective cohort study, which compared women who had abortions to women who did not, matched on key confounders, found no evidence for an increased likelihood of incident or recurrent mental disorders over the short (2.5 to 3 years post-abortion) or long term (5 to 6 years post-abortion)[88,89].

Although some studies have suggested a link between abortion and adverse mental health outcomes, they do not support causation, as they failed to adjust for pre-existing mental disorders and other confounders, such as pregnancy intention and intimate partner violence, and/or had other serious methodological flaws[82,85,89-93]. Such flaws include the inadequate measurement of exposure and outcome variables; the use of small, non-representative study samples; low response rates and high levels of loss to follow-up[94].

Women with mental disorders have been found to have a higher risk of unintended pregnancy or abortion[84,95]. A Canadian population-based study reported that, over a three-year period, women with schizophrenia had consistently higher abortion rates than those without this disorder (15.5-17.5 vs. 12.8-13.6 per 1,000 women, and 592-736 vs. 321-341 per 1,000 live births)[96]. Factors associated with increased abortion rates among women with schizophrenia included younger age, multiparity, comorbid non-psychotic mental disorder and substance use disorder.

A Finnish study which also used population-based data similarly found that women with schizophrenia had a higher rate of abortion than those without this disorder, also reporting that terminations performed after 12 weeks of gestation were more prevalent among women with schizophrenia[97]. This study additionally found that the majority of abortions were conducted for social rather than medical reasons.

Several potential mechanisms underlie the above association[61,98-100]. For example, mental disorders can impact contraceptive choices or adherence, increase the risk of sexual coercion, and, in women with conditions such as bipolar disorder, lead to hypersexual behaviour. Moreover, amenorrhoea subsequent to antipsychotic-induced hyperprolactinaemia or to anorexia nervosa may lead women to erroneously believe that they are infertile and increase the risk of unintended pregnancy and abortion. Finally, for women with a mental disorder, pregnancy may more often be unwanted, potentially mediated by other factors such as socioeconomic circumstances and impaired self-efficacy[57,101].

Research has examined what predicts poorer mental health outcomes around the time of abortion (a question that is distinct to that of whether abortion increases the risk of mental disorder). While predictors of poor mental health outcomes among women undergoing abortion include prior mental disorder, unstable relationships and adverse experiences such as intimate partner violence[76,82,84,102], these are general risk factors for mental disorders, again suggesting that abortion itself does not pose specific risks for future mental health issues.

Abortion stigma and structural barriers to abortion access have also been identified as predictors of mental disorder among women having abortion[103-105]. Research has also examined the impact of restricting access to abortion services on the risk of mental disorder among women of reproductive age[106-109]. In the US, the Turnaway study found that those denied an abortion due to being just over the gestational limit had higher anxiety and stress symptoms and lower self-esteem eight days later compared to those who were able to get an abortion[76,110,111]. Among women eligible to participate in this study, 38% consented to participate, and attrition between baseline and 5-year follow-up was 42% for both groups – an impressive retention for such a long duration of follow-up – and the results were robust to appropriate sensitivity analyses.

Other longitudinal ecological studies conducted in the US, using difference-in-differences analyses, report that abortion restrictions are associated with increased rates of suicide and mental health symptoms among reproductive-aged but not older women[106]. While the design of these studies limits causal inference, these and similar findings suggest that limitations on reproductive autonomy may contribute to an elevated risk of mental disorder for women of reproductive age[106-109]. Indeed, women whose reproductive autonomy is most restricted or who experience most obstacles to abortion services are often those with fewer resources[107-109,112], and those who have been historically marginalized[113]. Ensuring safe and accessible

abortion services is of critical importance for women's mental health. Integrated care approaches are likely to be needed, especially for women with mental disorders, to reduce the risk of unintended pregnancy and subsequent abortion.

SEXUAL DYSFUNCTION

Sexual dysfunction is common among women in the general population, with an estimated 41% of women of reproductive age experiencing it during their lifetime[114]. It is characterized by symptoms such as reduced libido, difficulty with arousal and/or orgasm, and genito-pelvic pain or penetration disorder. Risk factors include lack of an intimate relationship, poor body image, low levels of sex education, younger age, lack of exercise, and early life trauma, particularly sexual abuse[115]. A satisfactory sexual life necessitates social interaction skills, an understanding and acceptance of one's sexual orientation, self-confidence, and adequate sexual physiology. Historically, women's sexuality has been undervalued[116-119], leading to limited investigation compared with men's sexuality.

Sexual dysfunction in women is commonly a symptom or manifestation of psychological distress or underlying mental disorders. For example, low libido is a cardinal symptom of depressive disorder, while increased sexual interest is common in mania, as discussed further below. Some treatments for mental disorders are also linked to increased risk of sexual dysfunction[120]. Overall, the prevalence of sexual dysfunction is increased in women with mental disorders, being found to exceed 60% in this group[121-124]. These women are also less likely to have their sexual and reproductive health attended to appropriately[125]. Some risk factors for sexual dysfunction overlap with those for mental disorder. Therefore, women who are at higher risk for mental disorder are also at higher risk for sexual dysfunction.

Normal sexual function involves a complex interplay of central and peripheral neurotransmitters, neuropeptides and hormones, as well as a range of psychological and socio-cultural factors. Many psychotropic medications impact neurotransmitters, affecting mood and sexual function, over and above the dysfunction that might be related to the illness itself. These include benzodiazepines, antidepressants, antipsychotics and mood stabilizers. Recreational substances, including alcohol, are also associated with sexual dysfunction[124,126-128].

Medications can affect sexual function through direct central nervous system (CNS) effects (e.g., dopaminergic increase resulting in increased libido), indirect CNS effects (e.g., sedation secondary to histaminic effects), and hormonal effects (e.g., dopamine blockade causing hyperprolactinaemia).

Dopamine and serotonin, both important neurotransmitters with respect to emotional and

mental functioning, play crucial roles in sexual function. Dopamine stimulates testosterone, the hormone of sexual desire (more so than oestrogen in women) in both males and females. Testosterone, in return, stimulates both dopamine and noradrenaline, which both have positive effects on sexual function. Increased sexual activity is therefore seen with dopamine agonists, and reduced sexual activity with dopamine antagonists. As dopamine is the main prolactin inhibitory factor, the reduction of dopamine results in hyperprolactinaemia, which causes low libido and hypogonadal states, with marked negative effects on vaginal response and orgasm[129,130]. Serotonin agonists are associated with sexual dysfunction, with 5HT2A receptor stimulation, in particular, being related to impaired sexual function, and 5HT2C stimulation to increased sexual function. In addition, serotonin stimulates secretion of prolactin, which is inhibitory to sexual function. It is estimated that, on average, 50% of people experience sexual side effects with SSRIs. A small percentage (3 to 5%) report persistent sexual dysfunction despite cessation of the medication. This condition, known as persistent post-SSRI syndrome, is marked by genital anaesthesia and pleasureless orgasm, and is less common in women than in men[131,132].

Thus, the relationship between sexual dysfunction and mental disorders is complex, and may be influenced by the presenting condition or have arisen as a result of treatment[133]. Managing sexual dysfunction is crucial to a satisfactory sexual life, treatment adherence, and better mental health. A sexual and reproductive clinical history before starting medication, as well as psychoeducation about potential sexual side effects, is recommended. Sexual function should be regularly monitored. Dose reduction or switching to medications with fewer sexual side effects can help manage psychotropic-related sexual dysfunction[128,134-137].

For antipsychotic-induced dysfunction, the use of aripriprazole as an alternative or (if unable to stop the current antipsychotic) adjunctive treatment has shown effectiveness[128,134,136]. For antidepressant-induced sexual dysfunction, higher doses of bupropion are supported by moderate-quality systematic review evidence[135]. Evidence to support the use of psychological therapies is sparse[138], although there are some randomized trials indicating improvements in sexual functioning using a cognitive behavioural approach[139]. There is also some limited evidence to support the use of sildenafil, particularly for sexual dysfunction related specifically to arousal[138]. Hormone therapy, for example with testosterone, is currently only considered in cases of sexual dysfunction characterized by reduced sexual desire[140]. It is known to increase libido, particularly in post-menopausal women, but with side effects such as hair loss on the head and hair growth on the body.

Broader socio-cultural and structural factors also influence women's sexual experiences, highlighting the importance of considering the broad range of social determinants of sexual and mental health[115]. Societies with greater gender inequality are marked by higher levels of sexual dysfunction in women. Women in male-dominated societies report worse sexual health

and less sexual satisfaction compared to those in more gender-equal environments. Different risk factors arise globally, influenced by social and religious contexts. For example, in some countries, polygamous relationships and having undergone female genital mutilation are associated with worse sexual function[115].

HYPERSEXUALITY

Hypersexuality refers to a pathological increase in sexual thoughts and behaviours[141]. It can occur in various mental disorders, but the ICD-11 now also includes a distinct diagnosis of compulsive sexual behaviour disorder, classified as an impulse control disorder. This disorder is defined as a persistent pattern of failing to control intense, repetitive sexual impulses or urges, leading to repetitive sexual behaviour over an extended period (i.e., six months or more) that causes marked distress and/or impairment in important areas of functioning, including the neglect of other alternative activities[17]. Other features include unsuccessful efforts to reduce the behaviour, and its persistence despite adverse consequences and/or deriving little or no satisfaction from it.

Epidemiological data on the prevalence of compulsive sexual behaviour disorder in women are scarce, but studies suggest that it is far less common than in men, with a male-to-female ratio of about 3:1[142]. Population-level estimates (not aggregated by gender) range from 1 to 6%[143].

The dopaminergic system is implicated in the pathophysiology of the disorder[142]. Indeed, use of dopamine agonists is associated with compulsive sexual behaviour[144]. There may be links to adverse childhood experiences, such as abuse (although more commonly associated with sexual avoidance), underpinned by epigenetic changes in the corticotropin-releasing hormone gene and hypothalamic-pituitary-adrenal (HPA) axis dysregulation[142]. However, most research in this area has been conducted in men. Attachment difficulties, which are also associated with early exposure to sexual abuse, have been implicated in both male and female samples[142].

Social factors, such as societal attitudes towards sexuality, including religiousness and moral conservatism, are also correlated with the disorder[142]. Moral incongruence, where individuals engage in behaviours they disapprove because of their moral beliefs, may also explain the tendency to attribute these behaviours to an addiction, increasing the likelihood of seeking medical attention[145]. The ICD-11 definition clarifies that distress about sexual behaviour arising exclusively from religious or moral concerns is not enough to justify a diagnosis of compulsive sexual behaviour disorder[17].

Hypersexuality may also arise in the context of other mental disorders. The ICD-11 lists

"increase in sexual drive" among the symptoms of mania[17], while the DSM-5 refers to hypersexuality both within "increase in goal-directed activity" and "excessive involvement in activities that have a high potential for painful consequences" when describing manic episode[18]. For some individuals with bipolar disorder, subtle changes in sexual drive may be an early warning of a manic or hypomanic episode[146]. Studies have observed an increased frequency of sexual intercourse in people with mania[147], and people with bipolar disorder may engage in more frequent extramarital affairs[148-152] and changes of sexual partner[153]. A review highlighted gender differences in the incidence and severity of risky sexual behaviour in bipolar disorder, with women engaging in more dangerous behaviours during manic or hypomanic episodes compared to men[154]. Hypersexuality may also occur in borderline personality disorder, in which sex is listed as a potential area of impulsivity in both the ICD-11[17] and the DSM-5[18]. For a diagnosis of compulsive sexual behaviour disorder, sexual behaviour must be persistent, independent of mood episodes, and not be explained by other organic conditions (e.g., dementia) or use of substances (e.g., cocaine or methamphetamine)[17,143].

Management of compulsive sexual behaviour disorder primarily involves psychological intervention, with no pharmacological therapies specifically licensed for it (although plenty are used to treat comorbid psychopathology, the evidence for which is confined to case studies)[155]. Similarly, evidence for psychotherapeutic approaches is sparse[144], with a 2020 systematic review highlighting a complete lack of high-quality literature[156]. Some studies have examined the effectiveness of psychoeducational, cognitive behavioural, and acceptance and commitment approaches, but these have involved predominantly male samples[156].

An emerging qualitative literature describes the experiences of women who have undergone periods of hypersexuality, with many reporting significant shame, particularly in parts of the world with more stigma related to women's sexuality[146]. In some cases, hypersexuality and its consequences (which may include sexual assault) may be associated with PTSD[157,158]. Yet, like other areas of women's sexual functioning, the experience and phenomenology of hypersexuality is understudied. In borderline personality disorder, most research has focused on sexual impulsivity, which is conceptualized as both an increased number of "casual" sexual partners and an earlier age of first sexual intercourse, with more evidence for the former[159]. In bipolar disorder, it remains unclear the extent to which hypersexuality is experienced in women as increased sexual interest alongside increased energy and disinhibition, or it results from increased impulsiveness and risk taking.

Regardless of its aetiology or underlying diagnosis, it is important that hypersexual behaviour is identified by health care professionals, because of its potentially devastating impacts on individuals, partners and families, including increased risks of sexual abuse and exploitation.

SEXUAL VIOLENCE AND REPRODUCTIVE COERCION

Sexual violence refers to any sexual activity that happens without consent, regardless of the relationship between the perpetrator and the victim, and the setting in which it occurs. It includes (but is not limited to) rape, sexual exploitation, sexual assault, sexual harassment, and indecent exposure. Reproductive coercion intersects closely with, but goes beyond sexual violence, aiming to "maintain power and control in a relationship related to reproductive health"[160]. It may be perpetrated by intimate partners or family members, and disproportionately affects women and girls of reproductive age[161,162]. It encompasses manipulation, emotional blackmail, threats, and various forms of abuse (physical, sexual or financial) that can be promoting pregnancy (e.g., contraception sabotage, forced sex to cause pregnancy, pressured or forced continuation of pregnancy) or preventing pregnancy (e.g., pressured or forced sterilization or use of contraception, pressured or forced abortion, physical violence to induce miscarriage)[163-166]. It is associated with an increased risk of unintended pregnancy, increased severity of intimate partner violence during pregnancy, and intimate partner homicide[167].

Sexual violence is pervasive globally. In the US, the National Intimate Partner and Sexual Violence Survey indicates that 19% of women have experienced rape in their lifetime[168]. In Europe, the European Union Fundamental Rights Survey found that 5% of women had been raped since age 15, with varying rates across countries, ranging from 4 to 17%[169]. Technology-enabled sexual violence is also emerging as an issue of concern: recent research conducted in the UK, Australia and New Zealand found that more than one third of participants in an online panel survey of general community members aged 16-64 years had experienced image-based sexual abuse since age 16[170]. An analysis using Global Burden of Disease data indicates that, although there has been an overall decrease in the rate of sexual violence over time, the rate of decline is slow. In low human development index countries, the trend has been one of increasing sexual violence against women[171].

The prevalence of reproductive coercion in women and adolescent girls ranges from 8 to 30%, with 1 to 19% experiencing pregnancy coercion and 7 to 15% contraceptive interference[164,165,172]. Evidence from low- and middle-income countries is relatively scarce, but studies from Ethiopia, Kenya and India report prevalences from 11 to 28%[173-177]. Risk factors include young age, single status, being non-White, living in poverty, being less educated, and having a partner who has other concurrent partners[172,176,178]. Migrant and refugee women may also be more susceptible[179,180]. US data suggest that women with disabilities face up to a four-fold increased risk[181]. Reproductive coercion is of particular concern in gender-unequal societies, where other intersecting forces – including those based on ability, race and sexual orientation – are involved[182]. Investigation of the epidemiology of reproductive coercion is

hindered by the conceptual ambiguity and inconsistent measurement of this form of abuse[164,165,176,179].

Both sexual violence and reproductive coercion have a close (likely bidirectional) relationship with mental health. Risk of sexual violence is particularly high among women with mental disorder. In one study, 61% of women with severe mental illness had experienced sexual violence in adulthood (including 10% in the past year) versus 21% of women in the general population[183]. Research conducted in sexual assault referral centres in England (which provide a single point of access for people who have experienced sexual assault) suggests that up to 40% of attendees are already known to mental health services[184]. Women who experience sexual violence are also at significantly greater risk of mental disorder. The impact of sexual violence goes beyond PTSD to encompass a range of other mental disorders[185,186].

Research has attempted to identify risk and protective factors for mental disorder following sexual violence. Risk appears to be similar across demographic groups, but some assault characteristics appear relevant: weapon use and physical injury are associated with higher risk of mental disorder[186]. There is mixed evidence on whether the characteristics of the perpetrator influences risk for mental disorder in women. While a meta-analysis found that stranger-perpetrated sexual violence was associated with a higher risk of psychopathology in women[186], a more recent study indicated higher risk of depression in women from partner-perpetrated sexual violence[187].

Suicidal ideation and attempts are also more common among survivors of sexual violence[186]. Suicidality is more strongly associated with sexual violence than with other types of traumatic experiences, and the association appears to be independent of other comorbid disorders[188]. Although associations between sexual violence and substance use have been documented, prospective studies that control for pre-assault drinking do not indicate an increased risk of substance use following sexual assault[189,190].

Proposed mechanisms linking sexual violence and mental disorder include direct distress from the violence, negative social experiences such as lack of support and blame, and biological repercussions such as HPA axis dysregulation[191]. Pre-existing coping strategies, genetic vulnerability to mental disorder, and heightened vulnerability of people with mental disorder to sexual violence are also likely to be important[186,191-194].

Studies similarly report associations of reproductive coercion with depression, anxiety, PTSD and substance use[195-197]. There is evidence that mental disorder may moderate the outcomes of reproductive coercion. For example, PTSD and depression could diminish women's self-efficacy, potentially creating a barrier to the use of effective contraception and resulting in unintended pregnancy[198]. Risk is also increased where the economic deprivation and stigma associated with living with mental disorder forces people into vulnerable situations

and exploitative relationships, limits access to protective services, and reduces ability to escape abusive environments. Finally, it is important to acknowledge that mental health services may themselves be sites of sexual violence risk and further re-traumatization: a review by the UK Care Quality Commission of incidents on mental health inpatient wards identified more than 400 cases of sexual assaults or harassment of patients and staff over a three-month period, including 29 allegations of rape[199].

Enquiry about violence and abuse, including sexual violence and reproductive coercion, is an important part of the health system response. Enquiry should usually be conducted in private settings, excluding intimate partners, family and carers[200]. The World Health Organization (WHO) and the World Psychiatric Association (WPA) recommend a LIVES approach (Listening non-judgmentally and empathically; Inquiring about needs and concerns; Validating experiences; Enhancing safety for victim and family; and Supporting and connecting to information and services)[201]. Health care providers can also play an important role in responding to mental health concerns and offering empathetic and non-judgmental first-line support[202]. The social context is pivotal, with perceived social support and positive regard both important to recovery[203]. Many survivors experience feelings of shame and self-blame, and many report disbelieving, judgmental and stigmatizing attitudes from families, communities and services, which reduce willingness to disclose sexual violence and to access support[204-206].

Recently, the CARE (Choice and control; Action and advocacy; Recognition and understanding; Emotional connection) model was developed specifically as a survivor-centred approach to reproductive coercion, for practical and emotional support[207]. The ARCHES (Addressing Reproductive Coercion in Health Settings) intervention, though lacking a specific mental health focus, has shown promise in reducing reproductive coercion among women experiencing multiple forms of such abuse in US settings[208,209]. Mental health components in such interventions remain a crucial gap.

Technology-assisted interventions that strive to reinforce the importance of accessing health services may be an effective and scalable option, especially in university, school and community settings where rates of reproductive coercion, violence and mental disorder are notably high[210-212]. RCT evaluation of a free safety planning app (“myPlan”) found significant reductions in reproductive coercion and suicide risk over 12 months, suggesting some potential as a digital complement to broader responses aimed to support mental health among women exposed to violence and reproductive coercion[213].

Trauma-focused cognitive behavioural therapy and eye movement desensitization and reprocessing (EMDR) are evidence-based interventions to manage the trauma associated with exposure to violence and abuse[214]. Trauma debriefing is commonly practised, but evidence suggests that it does not prevent the onset of PTSD and may even increase risk[215].

Systematic review evidence highlights the importance of the context of psychosocial interventions in shaping how they are accessed and experienced by survivors[216]. These include organizational features, such as the setting or location in which interventions are delivered, and interpersonal factors such as being treated with warmth, kindness and respect.

Systematic reviews from both high- and lower-income settings report a range of psychological interventions that can improve mental health outcomes such as depression and PTSD[214]. However, there is little evidence on psychological interventions for other disorders, such as psychoses, or the extent to which the effectiveness of the interventions is moderated by recent, current or historical abuse.

INFERTILITY AND ASSISTED REPRODUCTION

Infertility is most commonly defined as an inability to conceive after at least 12 months of unprotected sexual intercourse[217]. Primary infertility refers to those who have never conceived, whereas secondary infertility, which is more common, describes those who have at least one child but have been unable to conceive again[217]. Social infertility describes people who are single or in same-sex relationships who require fertility treatment[218].

Infertility affects 8 to 12% of heterosexual reproductive age couples, rising to nearly 30% in low- and middle-income countries[219-221]. Male factors (for example anatomical abnormalities and sperm deficiencies) and factors related to women (for example uterine fibroids, endometriosis, and ovulatory dysfunction) each account for approximately 40% of infertility cases, with the remaining 20% unexplained[217,222].

Demand for infertility treatment has increased, due to delayed childbearing and improved treatment success rates[223], and is expected to continue rising[224]. Common fertility treatments include ovulation induction, OI (in which medications are used to stimulate the ovaries); intrauterine insemination, IUI (in which sperm is injected into the uterus); surgery (for example in endometriosis); and in vitro fertilization, IVF (in which the sperm and oocyte are combined in the laboratory to produce embryos, which are then transferred back to the woman's uterus)[217]. Multiple cycles of treatment are typically required, with up to six cycles of OI[225] and three or more cycles of IVF often recommended[217]. Women may start with less invasive treatments, such as OI or IUI, and progress to more invasive treatments such as IVF if needed. The treatment process can take years[226], and can significantly impact mental health, due to associated emotions of grief, loss, frustration and anger[222,223].

Women with infertility and/or undergoing treatment frequently experience symptoms of mental disorder[219,227]. Up to 78% report anxiety symptoms and up to 56% depressive symptoms[217,219,228-231]. There have been reports of transient psychosis with some infertility

treatments[232]. Other mental health consequences include sexual dysfunction, somatization, panic attacks, and eating disorders. Fertility treatments can cause physical side effects such as headaches, dizziness, sleeplessness, breast pain, and joint pain[217,223,227].

Emotions associated with treatment are amplified with multiple cycles[222], which can increase strain on relationships, finances and employment[217]. Approximately 30% of those undergoing fertility treatment will not achieve parenthood[233], and the decision to stop treatment represents a permanent loss of potential parenthood[222]. High psychological burden is a common reason for stopping treatment, even where there is a good medical prognosis and financial capability for further cycles[217,227,233].

The impact of psychological distress on treatment outcomes is unclear. While some women, and those in their social support network, believe that stress can cause infertility and reduce treatment success[234], two of three systematic reviews of emotional state and pregnancy outcome found no association[220,235,236]. Although a systematic review and meta-analysis of cortisol and pregnancy outcomes found associations in eight of twelve studies, the direction of these associations was mixed[237].

Psychological interventions such as cognitive behavioural therapy, mind-body interventions, counselling, yoga, relaxation, exercise, and positive reappraisal therapy can reduce depression, anxiety and stress, and enhance well-being in women with infertility[219,238-240]. Evidence on whether psychological interventions designed to reduce anxiety and depression in women with infertility lead to an increase in pregnancies is, however, mixed[220,230,238,240-247].

Women with affective and non-affective psychotic disorders exhibit lower fertility rates compared to those without these disorders and those with common mental disorders[248-250]. This has been attributed to several factors, including the impact of the illness on affect and behaviour, which can impair ability to form and sustain stable relationships, and medication side effects such as hyperprolactinaemia. The advent of second-generation antipsychotics, perceived to have fewer side effects impacting fertility, was therefore expected to improve fertility outcomes for women with psychotic disorders. However, a recent retrospective cohort study using UK data found similarly low pregnancy rates regardless of using first- or second-generation antipsychotics, with a notable increase in pregnancy rates upon discontinuation of these medications[251]. This may be due to confounding factors such as illness severity, with healthier women more likely to conceive and stop medication, or to the side effects of second-generation antipsychotics negating potential fertility benefits.

GYNAECOLOGICAL CONDITIONS RELATED TO FERTILITY

Some gynaecological disorders, including endometriosis and polycystic ovarian syndrome (PCOS), reduce fertility and significantly impact women's mental health.

Endometriosis is a chronic disorder, resulting from the presence of endometrium-like tissue outside the uterus, which affects up to 15% of women of reproductive age[252-256]. The aetiology is likely multifactorial, involving hormonal, genetic, inflammatory, environmental and immunological factors[253,254,257,258]. The main symptom is pain, with up to 83% of women experiencing pain during menstruation, sexual intercourse, urination or defecation and/or chronic pelvic pain[253,254,258,259]. Women may also experience heavy or irregular periods[253,254,259]. Other associated conditions include migraine, back pain, fibromyalgia, uterine fibroids, and ovarian cysts[257,259]. Treatments (including hormonal and non-hormonal medication, and surgery) aim to control pain, reduce recurrence, and improve physical functioning, but up to 59% report ongoing pain post-treatment[256,260,261].

PCOS is characterized by hyperandrogenism and menstrual irregularities, and affects up to 20% of women of reproductive age. It is associated with metabolic syndrome[262,263] and may also increase the risk of endometriosis via inflammatory mechanisms[264]. Treatments include lifestyle modifications to reduce the risk of metabolic syndrome, and hormonal treatments to reduce the symptoms of hyperandrogenism[263].

Both endometriosis and PCOS can affect women's mental health, due to the burden of symptoms, treatment, fertility concerns, and chronic pain, impacting multiple areas of life, including education, employment and caring[257,260,265,266]. Endometriosis is associated with an increased risk of depression (odds ratio, OR=1.9, 95% CI: 1.6-2.1) and anxiety (OR=2.4, 95% CI: 1.1-5.4)[258,260,262,263,267,268]. Women with PCOS are more likely to have at least one mental disorder compared to those without (OR=1.6, 95% CI: 1.5-1.6)[268-270].

Evidence from meta-analyses shows that women with PCOS have an increased risk of symptoms of depression (ORs range from 2.6 to 3.8)[263,269] and anxiety (ORs range from 2.7 to 5.6)[263,269]. There is also preliminary evidence of a relationship between PCOS and subsequent psychotic disorders from a study using a Northern Finland birth cohort (hazard ratio, HR=2.99, 95% CI: 1.52-5.82), with the hypothesized mechanism involving hyperandrogenism[271] and the protective role of oestrogen[272].

Increased risk of mental disorder may be related in part to the impact of PCOS on physical appearance[269,273,274]. There may be also a familial component, as higher rates of mental disorder have been found in siblings of women with PCOS, potentially explained by environmental factors, and alterations in androgen production or steroidogenic pathways[268]. There is also an established link between insulin resistance and depression[269,275]. Finally, inflammation underpins both endometriosis and PCOS and a number of mental disorders,

such as depression[258,267,276].

PCOS may be treated with SSRIs and/or hormonal therapies. Oral contraceptives are used in PCOS to treat symptoms such as body hair growth and irregular periods. While their use has been associated with improvements in some domains of quality of life, evidence of their effects on depression is mixed and requires further investigation[268,269]. If prescribing psychotropics in those with PCOS, it is important that metabolic side effects such as weight gain are carefully considered, given the increased risk of metabolic syndrome[263,269,274]. In both PCOS and endometriosis, the use of psychological interventions, including cognitive behavioural therapy, has been associated with improved well-being and reduced symptoms of anxiety and depression[252,263,276,277].

The close relationships between mental health, fertility and associated gynaecological conditions underpin the importance of an integrated approach to clinical management, research and health policy within this area. Only 35% of women with PCOS report discussing mental health with their primary care physician[268]. Regular enquiry about mental health in this population, and consideration of the impact of the conditions and their treatment is critical to providing holistic care[263,268,269,278]. Indeed, there is evidence that depression and anxiety can make it more difficult for those with PCOS to adhere to their treatment plan and engage in lifestyle interventions[263,268,276].

MENOPAUSE

Menopause is defined as the permanent cessation of ovarian function[279], usually indicated by the last menstrual period. The mean age of menopause is 51 years, but this varies widely among individuals and regions of the world[279,280]. The menopausal transition, characterized by menstrual cycle irregularities and hormonal changes, starts five to eight years earlier[281]; this period through to one year after menopause is also called “peri-menopause”. During these years, the ovarian production of oestrogens and progesterone decreases, often with significant fluctuations in blood levels[279].

Common peri-menopausal manifestations include vasomotor symptoms (hot flushes and night sweats, which can affect up to 80% of women), insomnia, poor concentration or “brain fog”, low mood and sexual dysfunction, including vaginal dryness, dyspareunia and reduced libido[282-285]. Symptoms can continue for years and significantly reduce quality of life[282]. The hormonal changes that accompany menopause can also negatively influence mental health, as oestrogens have neuro- and psycho-protective properties[286,287]. In particular, 17-β-oestradiol, the natural oestrogen that is most active in the brain, can modulate different neurotransmitter systems – including serotonin, noradrenaline, dopamine, glutamate and

acetylcholine[287-289] – with multiple effects on mental functioning[287,290,291]. The presence of 17-β-oestradiol is also associated with improvements in affective symptoms[290,292-294] and cognitive functioning[283-285,292,295-299], as well as antipsychotic properties[272,299,300]. There is also evidence that menopause can impact brain structure and connectivity[301].

Research on the relationship between menopause and mental health suffers from a number of methodological limitations[302]. These include a lack of differentiation between menopause, peri-menopause and post-menopause; incidence and prevalence; mental disorders and symptoms; self-report and clinician assessments; and clinical and community-based samples. Furthermore, it can be challenging to ascertain what is "normal ageing" versus pathological change, and what may be attributable to hormonal versus psychosocial changes (e.g., losses and role transitions)[302,303].

The most methodologically sound studies suggest that peri-menopause (though not post-menopause) is a vulnerable period for depression: most longitudinal, population-based studies have reported an increase in depressive symptoms[304-307] and major depressive disorder, correlating with hormonal changes[304-307]. In a population-based cohort of 231 women aged 35-47 years without previous depression, followed up for eight years, new-onset depressive disorders were 2.5 times more frequent during the menopausal transition compared to pre-menopause[305]. Increased depressive symptoms correlated with higher FSH, LH and inhibin B levels, and greater variability of oestradiol and FSH levels, suggesting that, similar to PMDD, fluctuating rather than absolute hormone levels trigger depressive symptoms.

Likewise, in a population-based cohort of 643 women aged 36-45 years without previous depression, followed up for 36 months, there was a two-fold increase in depressive symptoms and disorders during the menopausal transition, especially in those with hot flushes[304]. Depressive symptoms were also associated with adverse life events[304]. A further two population-based cohorts of 3,302 and 221 women aged 42-52 years, followed up for ten years, observed a significant increase in depressive symptoms and a two- to four-fold increase in major depressive disorder in the peri-menopause and early post-menopause, independent of vasomotor symptoms or stressful life events[306,307].

One investigation that refutes this evidence was a prospective population-based cohort study of 168 women. While irritability and nervousness increased in peri-menopausal women, the prevalence of major depressive episodes did not increase. However, the study was not primarily designed to answer this research question, and only 27% of the sample had reached menopause at the time of assessment[308].

Although there remains some ongoing debate surrounding the relationship between menopause and depression[309], the main risk factor in the peri-menopause appears to be a history of prior depression, particularly related to hormonal changes, for example depression occurring during peripartum or PMDD[310,311]. This suggests that belonging to a subgroup

sensitive to oestrogen withdrawal increases the risk for developing depressive symptoms during menopausal transition[312]. Women who suffer from hot flushes, sleep disturbances or vasomotor symptoms also seem to be at increased risk for depressive symptoms[306,310]. The risk is also higher in women who have a very late or prolonged menopause[313,314], or an abrupt surgical menopause with no hormonal substitution[313]. Psychosocial stressors, such as financial difficulties and lack of social support, are additional risk factors and interact with biological changes[304].

There is some evidence of an increased risk of new-onset psychotic disorders following menopause, supporting the "oestrogen protection hypothesis", which postulates that oestrogens are protective against psychoses[315]. In a representative sample of 392 first-admitted patients with psychoses, incidence was higher for young men than for young women but, after age 40, women experienced a second peak of onset, with an incidence about twice as high as in men[316]. These women also had more severe symptoms and a worse course of illness. Epidemiological studies have since confirmed these findings[287,317]. A recent systematic review also concluded that menopause can have a significant impact on women with schizophrenia spectrum disorders, with changes in symptomatology, cognitive function and quality of life[318]. An effect of menopause on the pharmacokinetics and pharmacodynamics of antipsychotics, with consequences on their bioavailability and on response to treatment, has also been reported[319].

Hormone replacement therapy (HRT) has traditionally been associated with managing physical menopausal symptoms, in particular vasomotor ones[279]. This therapy, particularly transdermally applied 17-β-oestradiol, seems also to improve depressive symptoms and may reduce the risk of major depressive disorder, especially if onset is during peri-menopause[320-323]. HRT is not officially approved for the treatment of menopausal depression either in Europe or the US, but clinical guidelines recommend its use for low mood, especially in peri-menopausal women with vasomotor symptoms[321-323]. 17-β-oestradiol may also have indirect positive effects on mental well-being by attenuating peri-menopausal complaints such as hot flushes, night sweats with sleep disturbances, and general irritability. It may thus contribute to a general improvement of the mental state, and to prevention of relapses.

Concerns about risks of treatment have led to controversy about oestrogen replacement. New studies, however, as well as re-analyses of earlier data (e.g., from the Women's Health Initiative study) suggest benefits when oestrogen replacement is started early in a so-called "window of opportunity"[324]. An individual risk-benefit assessment is always necessary (including comparison with psychotropics), alongside close monitoring by an expert[321-327]. Alternatives such as selective oestrogen receptor modulators might also ameliorate symptoms in post-menopausal women with schizophrenia or depression[302,328]. However, results so far are inconsistent. SSRIs can ameliorate both depressive symptoms and hot flushes, and their

augmentation with oestrogens seems particularly effective[329].

Psychotherapy is especially important, because this phase of life is often characterized in women by numerous psychosocial stressors, such as the realization of ageing, role transitions, and sexual and relationship difficulties. It may also be a period in which women feel the need to re-evaluate their life expectations, with gender stereotypes often having prevented them from pursuing their goals. Psychotherapy in this age group should also pay attention to women's subjective experience of the menopause, including their physical complaints, their fears and beliefs regarding menopause and the changes experienced, as well as their femininity and sexuality[303].

Cognitive behavioural therapy is recommended and has been adapted for menopause[322,330]. A meta-analysis of 14 RCTs found small-to-medium effect sizes for reductions in symptoms of depression and anxiety[331]. Empowerment and the development of self-confidence are essential elements of therapy[303,309,332,333]. Empowerment can also be achieved through education about menopause[332]. Given the range of physical and mental symptoms that women may be experiencing, an integrated approach considering both biological and psychosocial treatments, and tailored to individual needs, is essential.

IMPLICATIONS FOR RESEARCH

Women's reproductive mental health is under-researched. Stigma and societal taboos surrounding women's reproductive health may have contributed to this[12], along with a lack of women scientists in senior academic positions[10]. Another contributing factor may have been the negative findings of the early studies on women's hormones and mental health, due to their focus on between-person differences, as opposed to the growing body of recent research which has focused on within-person differences, highlighting the critical role of hormonal fluctuations in the genesis and maintenance of mental disorders, within the broader socio-cultural milieu[11]. A "sex and gender neutral" approach, failing to consider this component in the design, conduct and reporting of mental health research, risks undermining its scientific validity and efficiency. This in turn impairs the delivery of sex- and gender-sensitive mental health treatments and services.

Global inequalities in research capacity and in health care access pose challenges to the generalizability of what remains a limited evidence base. Many of the studies on women's reproductive mental health have been conducted in high-income countries, and translating findings to low- and middle-income contexts remains problematic. For some of the issues that are not experienced exclusively by women, for example hypersexuality and sexual dysfunction, there remains a preponderance of studies focused only on men. Moreover, there

is a lack of research on how the lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ+) and gender diverse communities experience reproductive mental health issues, including sexual violence, reproductive coercion, and infertility. Addressing these disparities is crucial for advancing understanding of and addressing reproductive mental health issues[218].

Women's reproductive mental health involves complex interactions of biological, psychological, social, cultural and political factors, necessitating interdisciplinary collaboration across fields such as psychology, obstetrics/gynaecology, psychiatry, public health, psychoneuroendocrinology and sociology. Such collaborations can drive innovative methodologies and interventions, shedding light on the mechanisms underlying mental disorders and guiding therapeutic approaches. Research is also urgently needed on the indications and contraindications of hormonal treatments for women with mental disorders, especially on the relative risks of hormones compared to psychotropics and/or the best augmentation strategies.

Social and structural determinants are likely to moderate the mental health impacts of reproductive events. Understanding their trajectory will require longitudinal research. To facilitate this, there needs to be routine data collection on exposure to the social determinants of mental health. Research should ensure the measurement and analysis of their impact in trials of (pharmacological and non-pharmacological) interventions, in observational cohort studies, and in the evaluation of public health interventions. More broadly, work is needed to improve the methodological rigour of research, addressing issues such as inconsistent measurement and conceptual ambiguity. Greater use of subgroup analyses is needed to identify specific risk factors, protective factors, and differential intervention effects based on demographic, clinical and contextual factors.

Investigating the complex and multifaceted sexed and gendered determinants of mental health, including those relating to reproductive life events, is essential for advancing understanding and treatment of mental disorders, benefiting women and society as a whole.

IMPLICATIONS FOR CLINICAL PRACTICE AND HEALTH POLICY

The intersection of women’s reproductive and mental health, along with their complex biopsychosocial underpinnings, underscores the need for a holistic approach among clinicians caring for women of reproductive age, and among health policy makers considering how to respond to the increasing burden of mental disorder in this population[334]. Such an approach must account for both physical and mental health aspects, as well as for the broader social and economic contexts shaping women’s experiences.

Policy change is needed across numerous domains, spanning menstrual health,

contraceptive access, abortion rights, sexual violence prevention, trauma-informed care, fertility treatment access, and menopausal health care. Changes should seek to address social determinants of women's reproductive mental health, dismantling structural barriers, and safeguarding women's reproductive autonomy and mental well-being.

Health services need to be able to respond to the reproductive mental health care needs of their populations, including through the provision of gender-sensitive care. In particular, mental health clinicians should seek opportunities to enquire about reproductive and sexual health, including menstruation, sexual abuse, and access to reproductive interventions such as abortion and hormonal treatments, recognizing their potential impact on mental health. Evidence suggests that many health care professionals avoid these conversations, due to barriers such as lack of knowledge or uncertainty about how to approach them[335,336]. Overcoming these barriers necessitates ongoing training and workforce development, alongside the integration of information on women's reproductive and sexual health, and how this relates to mental health, into undergraduate and postgraduate curricula, particularly within psychiatric and gynaecological clinical training. It is also critical for prescribers to understand the interaction of psychotropic medications with sex hormones, and how such hormones can be used in clinical practice either as a first step or as an adjunct to existing treatments.

For many women, reproductive life stages may represent important transitions, accompanied by changes in their life circumstances and how they are viewed by themselves and others. Such transitions may provide a catalyst for seeking psychological help. Interventions can be offered at a range of intensities, though psychological therapies differ substantially in their availability worldwide. As a relatively simple and low-cost intervention, there is evidence that psychoeducation about the impact of reproductive life events on mental health can improve outcomes, including response to treatment[277,303].

Trauma is a shared mechanism mediating and/or moderating many of the relationships between reproductive life events and mental health examined here. There is increasing recognition that practices within mental health care – including but not limited to the use of coercion, seclusion and restraint – can be distressing and harmful to those with histories of trauma[337]. Trauma-informed care aims to reduce this risk of re-traumatization[338]. The implementation of trauma-informed interventions and services within mental health care, including the provision of single sex wards, needs urgent evaluation, with input and leadership from trauma survivors[165].

Health policies must support clinicians and health services to deliver integrated and holistic reproductive and mental health care at all points of contact with health services. Ensuring equity of access by women to reproductive and mental health care remains a significant challenge, particularly for marginalized groups, including women with substance misuse, personality disorder, or socio-economic deprivation. Additionally, understanding the

needs and experiences of diverse groups – including racially minoritized, gender diverse, neurodiverse, and LGBTQ+ individuals[339] – is imperative. Health services are often located in cities, leaving women from rural areas and Indigenous communities without access to these services, especially if there is unreliable transport and/or poor mobile phone coverage. However, integrating mental and reproductive health care also presents opportunities, given the prevailing prioritization of physical over mental health care in many regions[340]. Seeking assistance for reproductive health could provide an opportunity to address mental health concurrently.

Finally, stigma remains a significant issue for both mental and reproductive health[40,341]. Societal misconceptions and discriminatory attitudes surrounding mental health conditions and reproductive health choices persist, contributing to feelings of shame, secrecy, and reluctance to seek help. Women, in particular, often face societal judgments and cultural taboos regarding their reproductive health decisions, further exacerbating the stigma surrounding these issues. Moreover, the intersectionality of stigma compounds the challenges faced by marginalized groups, including racial and ethnic minorities, LGBTQ+ individuals, and those from low-income backgrounds. Addressing stigma requires multifaceted approaches, including public education campaigns, destigmatizing language and portrayals in media, and fostering supportive and inclusive health care environments where individuals feel empowered to seek the care they need without fear of judgment or discrimination.

CONCLUSIONS

Reproductive health is foundational for women's mental health and well-being. Violations of reproductive rights – including lack of access to reproductive health care, reproductive coercion and a lack of gender-sensitive mental health care – can lead to enduring negative mental health outcomes. Psychiatrists are well placed to advocate on behalf of their patients for access to reproductive health care, and also need to ensure that they have the knowledge and skills required to respond to their patients' reproductive health care needs.

By examining the interface between reproductive and mental health, we have highlighted in this paper urgent gaps in research, clinical practice and health policy that need to be addressed to optimize women's health. A concerted interdisciplinary effort is critical to advance the reproductive mental health field, to identify new therapeutic avenues and foci for interventions, and to improve quality of life for women globally.

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