Here lies the trouble. There are women who mimic fatigue, who indulge themselves in rest on the least pretence, who have no symptoms truly honest that we need care to regard them. These are they who spoil their own nervous systems as they spoil their children . . . that is a woman to order out of bed and to control with a firm and steady will. That is a woman who is to be made to walk with no regard to her complaints, and to be made to persist until exertion ceases to give rise to the mimicry of fatigue. (Mitchell, 1884/2015 p. 13)

The history of women and psychopathology is fraught. For centuries, women’s mental health and emotional risk have been integrally tied to the social construction of gender, conceptions of the “weaker sex,” and assumptions of lower female intelligence, competence, and moral capacity. In 1871, physician S. Weir Mitchell arrived at the conclusion that education and intellectual activity were a partial root of women’s psychological problems—“Our growing girls are endowed with organizations so highly sensitive and impressionable that we expose them to needless dangers when we attempt to overtax them mentally,” he concluded (Mitchell, 1871, p. 57). A decade later, in his groundbreaking treatise on female nervous disorders, Mitchell advocated a treatment plan involving extreme social isolation, a fat-rich diet, and frequent massage and described his patients as “morally degraded” and “basely selfish” (Mitchell, 1884/2015, pp. 8–9):

Against this historical backdrop, research on women and psychopathology has evolved in heartening ways. Yet much of this evolution has occurred outside psychological science. Although the conjunction of reproductive and mental health has been considered extensively within the fields of medicine, sociology, anthropology, and gender studies, this topic is understudied within psychology. Very few psychological scientists, even those

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who prioritize broad, integrative research, consider the importance of reproductive change. By neglecting one of the most basic facets of women’s lives, our field has left fundamental questions unanswered. In this introduction to the special series, we explore the reasons for this underrepresentation within psychological science, review recent findings and methodological developments in this field, and advocate for a new generation of dialogue and scholarship on women and mental health.

Reproductive Change and Mental Health: What Do We Know?

All animals have reproductive systems, and it is an evolutionary fact that these systems change over time as organisms develop, mature, and respond to their surroundings. In humans, this change is regulated by the endocrine system and manifests in women in two ways: in terms of significant reproductive milestones—such as the onset of puberty, pregnancy, and menopause—and in terms of smaller, continual fluctuations in hormones across the menstrual cycle. Because the secretion of reproductive hormones is regulated by the hypothalamus and because reproductive hormones act throughout the brain (e.g., McEwen, 2002), reproductive functioning is integrally connected to neural functioning. In this article, we use the terms reproductive development, reproductive health, and reproductive change interchangeably to denote both the larger, developmental milestones of the reproductive system and the continual intraindividual fluctuations in endocrine functioning associated with the menstrual cycle.

In women, epidemiological links between reproductive change and risk for psychopathology are clear. At puberty, girls show steep increases in clinical symptoms across a variety of psychological domains, including internalizing, aggression, delinquency, self-injurious behavior, substance use, disordered eating, school failure, and interpersonal conflict (reviewed in Mendle, 2014). Although boys also show significant emotional changes at puberty, all extant research suggests that puberty is more challenging and more widely associated with psychological distress for girls than for boys. Psychological symptoms continue to shift in relation to reproductive events (e.g. menstrual cycle, childbirth, menopause) across women’s lives. This occurs not just in America and other Western, industrialized nations but on all inhabited continents (e.g., Africa: Hung et al., 2014; Asia: Tsai, Strong, & Lin, 2015; Patel, Rodrigues, & DeSouza, 2002; Australia: Patton et al., 2004; Europe: Kiesner, 2009; Stattin & Magnusson, 1990; South America: Rojas et al., 2007).

Although links between reproductive change and emotional health have been documented for numerous symptom domains and clinical profiles, the trajectory of sex differences in depression provides a striking example. Prepubertally, boys and girls have roughly comparable levels of depression, with some studies suggesting slight elevations in depression in boys relative to girls (Cryanowski, Frank, Young, & Shear, 2000; Mendle, Harden, Brooks-Gunn, & Graber, 2010). As noted before, symptoms of depression increase rapidly in girls during the early stages of puberty in a way that they do not for boys. By the midpoint of the transition, girls are twice as likely as boys to be depressed (e.g., Angold, Costello, & Worthman, 1998). Higher prevalence of depression among females persists through much of adulthood, with risk of depression rising sharply during the transition to menopause and then dropping noticeably postmenopause (Freeman, Sammel, Boorman, & Zhang, 2014). Indeed, despite the copious dialogue regarding sex differences in depression, one point has rarely been emphasized in the psychological literature: This gender difference is far narrower prepubertally and postmenopausally. It is most clearly evident during the period of the lifespan in which women have high—and fluctuating—levels of ovarian hormones.

For pragmatic reasons, even the most comprehensive longitudinal studies rarely consider the full trajectory of reproductive maturation. Yet although research realities may limit studies that truly follow women “from menarche to menopause,” there are no practical limitations on developing and testing more complete integrative theories. Nevertheless, there is not a single cohesive theory of sex differences in depression that follows women through the postmenopausal drop in symptoms. It is unclear if and how we can resolve questions about etiology and symptom maintenance when assessments are confined within a limited developmental range. This snapshot-in-time approach may be particularly problematic for discerning mechanisms. On the surface, the epidemiological trajectory mirrors natural fluctuations in hormones across the lifespan. However, the etiological and maintaining factors are likely more complex and interactive than a simple biological model, reflecting that reproductive transitions—like all major life transitions—are filled with inter- and intrapersonal shifts that hold psychological and social resonance and require adaptation.

A primary concern is that psychological science’s lack of attention to women’s reproductive lives has constrained prevention and intervention in meaningful ways. Consider, for example, that suicide assessment protocols address an array of risk factors, including diagnostic vulnerability, history of previous attempts, a plan that is both lethal and viable, and current stressors (e.g., Linehan, Comtois, & Ward-Giesielski, 2012). Nowhere in the clinical training literature is the simple fact that suicide attempts in women are correlated with the menstrual cycle. For nearly 50 years, medical professionals have noted disproportionally high rates of suicide attempts and deaths during menstruation and early follicular phases of the cycle and dramatically lower rates midcycle (Baca-Garcia, Díaz-Sastre, de Leon, & Saiz-Ruíz,
changes are caused by various individual differences in that these risk-associated responses to ovarian hormone regenerative—and likely the most accurate one—would suggest a tricium; Ace & Okulicz, 2004). Therefore, a third perspective, too, is lacking because it fails to specify where these criticisms of the cyclical variations in hormones. Although there are legitimate concerns with overinterpreting the role of hormonal fluctuations in women’s emotional well-being, there is also an alarming dearth of strong, time-varying predictors of imminent suicide (Pearson, Claassen, & Booth, 2014).

To date, much of the research in psychiatry and related fields has respected disciplinary boundaries, effectively “fencing off” affective changes associated with reproductive events from general risk for affective pathology. There has been little attention to associations or differences between reproductive mood disorders (e.g., premenstrual dysphoric disorder, postpartum-onset depression, perimenopausal affective disturbance) and nonreproductively linked depression or anxiety. It is true that the psychological science of depression among women has not benefited as much as it should have from research in psychiatry, gynecology, endocrinology, and related fields that have focused specifically on reproductive mood disorders. But the converse is also true: The field of reproductive mood disorders has suffered from overreliance on categorization and diagnoses, in part because it has not benefitted from psychological science and its focus on dimensional symptoms, advanced approaches to studying change over time, and transdiagnostic mechanisms.

From a clinical psychological perspective, the basic issues that need to be addressed are who experiences difficulties associated with reproductive changes, why they experience those difficulties, and how we can help. The suggestion that hormones are fully responsible for sex differences in outcomes grossly oversimplifies the problem and assumes a homogenous response to hormonal changes, an assumption we now know is false (e.g., Schmidt et al., 1998; Vermeersch, T’Sjoen, Kaufman, Vincke, & Van Houtte, 2010). A second and more sophisticated model would suggest that individual differences in response to reproductive changes are responsible for the severe negative reactions to ovarian steroid changes seen in some women (Schmidt et al., 1998). This approach, too, is lacking because it fails to specify where in the body this response is occurring. There are hundreds of proteins across the body that are regulated by ovarian hormones (e.g., the expression of over 100 genes are regulated only by progesterone, only in the endometrium; Ace & Okulicz, 2004). Therefore, a third perspective—and likely the most accurate one—would suggest that these risk-associated responses to ovarian hormone changes are caused by various individual differences in how a woman’s brain and body react to the interactive effects of multiple hormones across multiple tissues—individual differences that are determined by a complex interplay of sociocultural and biological factors. As we discuss later, however, this model is too rarely represented within scientific dialogue.

**Why Is Reproductive Development Understudied in Clinical Psychological Science?**

If reproductive change can play such a vital role in women’s risk for psychopathology, why is it not more widely integrated into clinical science? We believe there are three potential reasons. The first is a residual societal reluctance to discuss female reproduction. Although there have been groundbreaking shifts in public dialogues about postpartum depression (PPD), largely facilitated by candid self-disclosures of numerous public figures, other aspects of reproductive health, especially menopause and the menstrual cycle, are so infrequently discussed that cultural anthropologists have referred to them as “taboo.” Because reluctance to discuss female reproduction understandably seems to be more characteristic of males than females (reviewed in Johnston-Robledo & Chrisler, 2013), the problem is inadvertently magnified, as men are still overrepresented in tenured faculty psychology positions (National Science Foundation, 2015) and among primary investigators on National Institute of Mental Health–funded grants (Rockey, 2014).

A second, more complex reason may be ambivalence about the meaning of biologically based sex differences. At present, there is a tension within academic psychology that is reflective of a larger social tension: Acknowledging a biologically based role for reproductive functioning in psychopathology raises powerful concerns about gender equality and difference. There is a tenuous balance in understanding that women may be at risk on a biological level, while simultaneously recognizing that not all women suffer from these vulnerabilities and that biological vulnerabilities are embedded within a larger sociocultural risk profile. We suspect many scientists grasp this dichotomy and are appropriately concerned that nuanced scientific findings will be inaccurately simplified and overgeneralized by media, social media, policy initiatives, or other scholars in ways that reinforce troubling or reductionistic modes of thinking about women and mental health (reviewed in Chrisler & Levy, 1990; Johnston-Robledo, Barnack, & Wares, 2006).

Scientists who “opt out” of the conversation on women’s reproductive change and psychopathology may also be deterred by the tone of existing psychological research on this topic. Modern science may no longer advocate a fat-rich diet and social isolation as a cure for depression, but there are certainly articles—even recent
ones—suggesting that unconscious, evolutionary drives are responsible for observed correlations between the menstrual cycle and factors as diverse and complicated as voting beliefs (Durante, Rae, & Griskevicius, 2013), racial bias (Navarrete, Fessler, Fleischman, & Geyer, 2009), jealousy (Cobey et al., 2012), rational decision making (Lazzaro, Rutledge, Burghart, & Glimcher, 2016), and attractiveness of female research participants along numerous dimensions, as rated by male observers (Guéguen, 2012; Pipitone & Gallup, 2012; Roberts et al., 2004). Perhaps the most troubling feature of this work is that correlates of the menstrual cycle are generally framed as universal and adaptive and rarely discussed in terms of possible confounds, individual differences, or the possibility that cycle effects may be driven by a smaller number of women with a maladaptive sensitivity to hormone change. Given these perspectives, it is unsurprising to find an opposing area of scholarship arguing that biological sex differences either do not exist or do not matter (e.g., Joel et al., 2015) or that reproductive mood disorders are merely cultural byproducts and should not be studied as distinct clinical entities (reviewed in Hartlage, Breaux, & Yonkers, 2014).

The truth, of course, is that accepting complexity is essential for psychological science. Biological differences exist, and they absolutely matter—to some degree. Social contexts also matter. Risk for psychopathology is intrinsically linked to life stress, and women are disproportionately at risk for traumatic stressors, particularly physical and sexual assault, and are more likely to experience chronic strains that take a toll on daily well-being (e.g., Nolen-Hoeksema, 2001). The integration of sex-divergent biological factors (such as ovarian hormones) into models of psychopathology need not undermine the importance of sociocultural context in explaining female-biased rates of psychopathology, just as it need not undermine our belief in female agency. We do not believe that implicating a role for hormones into models of emotional health necessarily suggests that women lack intention or volition over their actions, nor does it eliminate the truth that women’s emotional well-being is meaningfully influenced by the context in which they live. It is our hope that psychological scholarship in the coming years will achieve the necessary balance between identifying, interpreting, and overinterpreting biological sex differences.

Finally, a third reason why reproductive development has been overlooked by clinical science may simply be more prosaic. Owing in part to methodological limitations at the time, early research in this area was hardly promising. Starting in the 1980s, studies began to test for hormonal differences across women with and without premenstrual syndrome/premenstrual dysphoric disorder (PMS/PMDD) (or related symptom profiles using different labels) and consistently found no significant mean-level differences in reproductive steroid levels or patterns across these groups (see, e.g., Rubinow et al., 1988; Rubinow & Schmidt, 1992). Similar studies testing for associations between hormones and affective and behavioral symptoms at puberty likewise provided weak or no support that hormones played a significant role in girls’ emotional well-being (Brooks-Gunn & Warren, 1989; Paikoff, Brooks-Gunn, & Warren, 1991; Susman, Dorn, & Chrousos, 1991; Susman et al., 1987; Warren & Brooks-Gunn, 1989; see Angold, Costello, Erkanli, & Worthman, 1999, for an exception). As a result, many scholars concluded that reproductive hormones did not play a key role in the affective changes experienced by adolescent girls or in the sex difference in mood disorders. This perspective was particularly emphasized in two important review papers (Hankin & Abramson, 2001; Nolen-Hoeksema & Girgus, 1994), contributing to a shift within psychological science away from studies incorporating hormonal measurements. It should be noted that these authors were conducting sophisticated and cutting-edge research for the time but without the benefit of 20 additional years of methodological and statistical advancement that we now have.

A growing body of more recent scholarship illustrates that studies that incorporate only main, between-person effects of hormones are subject to inflated Type II errors and create risk of wrongfully accepting a false null hypothesis. Therefore, whereas older studies testing for average hormonal differences across women often found no evidence of hormone-related vulnerability to psychopathology (Golub & Harrington, 1981; Laessle, Tuschl, Schweiger, & Pirke, 1990; Ramcharan, Love, Fick, & Goldfiend, 1992), more recent studies that incorporate within-person analyses are far more likely to find significant effects of hormones on a variety of psychological and behavioral processes, including mood disturbances (Eisenlohr-Moul et al., 2016; Kiesner, 2011), eating disorder symptoms (Klump et al., 2013), and externalizing symptoms such as interpersonal conflict and general impulsivity (Eisenlohr-Moul, DeWall, Girdler, & Segerstrom, 2015).

These findings suggest a need for methodological adaptations in how psychological scientists approach the study of hormones and behavior. To address and to answer core questions, we will need to develop complex multilevel frameworks for accommodating the many and varied biological pathways involved in reproductive changes across a woman’s lifespan, how these biological and physical changes result in experiential changes (morphological changes, physical comfort, physical pain, anxiety), how the world responds to these changes, and how environmental demands influence each woman’s experience of these changes. Building and testing such models is a daunting task. Yet the alternative is to consider simplistic models that ignore cross-level effects and interactions and will likely provide shallow insights and dead-end research endeavors. We believe the field is ready for this challenge.
Two new methodological advances, in particular, have helped accurately characterize when, for whom, and how (i.e., in which tissues of the body) reproductive steroids influence psychopathology in women. First, multilevel models (also referred to as hierarchical linear models, mixed models, random coefficient models, and random effects models) represent an especially promising analytic option. In these models, variance in risk for steroid influences on the momentary expression of psychopathology can be precisely modeled at the between-culture level (e.g., individualism), between-person level (e.g., early life experiences, personality, genotype), between-cycle level (e.g., higher or lower life stress than usual), and daily level (e.g., acute stressors, acute changes in steroid hormones). These models provide an excellent framework for testing the sort of integrative theories that are likely necessary to capture the intricate nature of reproductive hormone effects on female psychopathology. A cursory review of the literature reveals that very few existing studies have adopted this analytic complexity (see Eisenlohr-Moul et al., 2015; Racine et al., 2013, for exceptions). This is true for research that addresses all major reproductive transitions: puberty, the menstrual cycle, pregnancy and postpartum, and menopause.

Reproductive hormone experiments represent a second novel method for evaluating the causal role of steroid hormones in psychopathology. A variety of designs are possible and offer different levels of experimental control over (and clarity regarding the causal role of) the hypothalamic–pituitary–gonadal axis in mental health. Randomized controlled trials of oral contraceptives can examine the pathophysiologic role of hormone flux in mood disturbances (e.g., Halbreich et al., 2012). Similarly, randomized controlled trials of hormone replacement therapy during the menopause transition can disentangle the differential impact of role transition from the direct or interactive effects of ovarian steroid levels or changes. Another rigorous set of studies has used GnRH agonists such as leuprolide or buserelin to “shut off” endogenous ovarian hormone production temporarily while exogenous reproductive steroids are administered and precisely manipulated. Such experiments may seem extreme, but they have yielded some of the most convincing, critical evidence regarding the biological validity of reproductive mood disorders such as PMDD (Schmidt et al., 1998), PPD (Bloch et al., 2000), and perimenopausal affective disturbances (Schmidt et al., 2015). Collectively, these studies both confirm a pathophysiologic role of ovarian steroid change in female psychopathology and highlight the critical role of individual differences when considering the relevance of ovarian steroid change to female psychopathology.

It should be noted that nearly all of these sorts of experiments have been conducted by gynecologists and psychiatrists rather than psychologists, and this is reflected in the nature of the research. Specifically, this work has focused on categories (“reproductive mood disorders” vs. controls with no psychopathology) rather than dimensional expressions of risk. It has generally utilized assessment instruments that have been under- or unvalidated for studying change as well as simplistic statistical models that do not incorporate an array of potentially important factors. Given their more extensive training in assessment and psychometrics, statistical modeling, and theories of psychopathology, psychologists would bring much-needed expertise to these projects, especially in conceptualizing between-person and environmental risk factors.

The Current Series

Our goal in this special series is to offer a sequence of articles that provide a cohesive introduction to this intricate topic, spanning the entire period of women’s reproductive change. The series opens with Alloy, Hamilton, Hamlat, and Abramson’s (2016, this issue) insightful exploration of sex differences in depression and anxiety at puberty. This article considers established cognitive mechanisms of adult depression and integrates them into the stage in life when sex disparities in depression first emerge. In addition to answering more general questions about puberty and depression, Alloy et al. explore individual differences in pubertal timing and highlight that early maturing girls’ greater tendency to ruminate during the pubertal transition may explain their disproportionate vulnerability to depression.

The benefits of innovative research designs are illustrated through the next two articles. Kiesner, Mendle, Eisenlohr-Moul, and Pastore (2016, this issue) employ sophisticated, within-person quantitative methods to highlight individual differences in the magnitude and direction of changes in physical and affective symptoms and cognitive style across the menstrual cycle. Results emphasize the substantial between-person variability in cyclical emotional and cognitive risk for psychopathology, underscoring the notion that cyclical changes in affect and attributional styles are common but hardly ubiquitous. Likewise, Klump et al. (2016, this issue) creatively adapt the classical twin design to investigate how differences in exposure to endogenous estrogen and progesterone moderate genetic and environmental influences on emotional eating. This innovative use of the twin design highlights the unique roles of reproductive steroids, shared and unique environmental contexts, and their interactions in risk for eating disorder.

The next two articles target specific transitions. Dunkel Schetter, Saxbe, Cheadle, and Guardino’s (2016, this issue) article on stress and PPD represents one of the only prospective attempts to explore PPD across multiple pregnancies. Dunkel Schetter et al. identify several, potentially malleable mediators that explain recurrence of PPD. These findings hold clear, real-world implications for women with...
histories of PPD who may be grappling with major life choices regarding future childbearing. Finally, Gordon, Eisenlohr-Moul, Rubinow, Schrubbe, and Girdler (2016, this issue) introduces and supports a novel framework for understanding the perimenopausal rise in depression, implicating hypothalamic–pituitary–adrenal functioning. Notably, Gordon et al.’s contribution demonstrates the unique perimenopausal vulnerabilities of women currently experiencing perimenopausal depression versus euthymic women with histories of depression. These results are congruent with findings on other reproductive transitions, in which moderation of within-person change by between-person factors represents the rule rather than the exception.

Collectively, these articles call attention to several key recurring themes: the continued impact of life stress, the importance of within-person processes, and the intersection of reproductive transitions with epiphenomena such as rumination, attributional style, or emotional eating. Our hope is that this series will highlight and correct misconceptions about the role of reproductive change in psychological health and convey the value of this topic to readers who may be less familiar with it. Yet it is worth noting that the questions and findings of the articles presented here go beyond female reproductive development. Understanding how psychological symptoms change at major life transitions, how social contexts intersect with genetic propensities, and how gonadal hormones influence brain and behavior are questions with broad interest and implications and are not limited to a single sex or a small set of psychological changes.

In our introduction to this series, we have situated our discussion of women and psychopathology within broader historical perspectives. But it would be naïve to suggest the articles in this series are free of the chronological limitations of the time period in which we now live. Indeed, it is likely that an academic in 2070 will read the scholarship presented here and marvel at how much we may have missed or misunderstood on this topic. Ultimately the questions that need to be addressed within future research will require more sophisticated theoretical models incorporating multiple levels of influence and interaction and the possibility of integrating biological and social environmental pathways across developmental and reproductive life events. These “possibilities” have the best chance of advancing the field if the theory driving them represents a fundamental shift in how we have traditionally conceptualized the topic of mental health. A truly integrative approach, targeting the entire lifespan rather than segmenting it, will bolster extant findings from endocrinology and psychiatry through the insights of psychological science and contribute not just to academic research but also to changes in social discourse. We have nothing but excitement for the future science of psychopathology and reproductive development—and we hope that some of the readers of this series play an active role in its creation.

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Note
1. Given the general focus of this series on reproductive functioning in relation to naturally occurring changes in endogenous ovarian hormones, we use the term women to refer to the female sex rather than the female gender. However, it should be noted that transgender women experience elevated risk for psychopathology, in part due to minority stress (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013), and that their experiences have also been underresearched within psychological science.

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