Women's Pleasures, Women's Pains: Oxytocin, Orgasm, and Endometriosis

by

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Abstract

The capacity for health and disease, and pleasure and pain, has an evolutionary legacy. Human females demonstrate a suite of unique as well as elaborated reproductive traits, such as invasive placentation, copious menstruation, and highly developed social cognition and cooperative breeding. These phenotypes involve coordinated psychological and physiological components that develop and express via environmentally sensitive neuroendocrine mechanisms, such as the oxytocin system and its interactions with gonadal hormones. An evolutionary medicine framework illuminates why these reproductive phenotypes are vulnerable to dysregulation, generating patterns of disease risk in women. I apply principles of evolutionary biology and evolutionary medicine to investigate female reproduction and sexual response as related to health and disease across four chapters. First, I review and synthesize several disparate bodies of literature to evaluate the hypothesis that elevated oxytocinergic activity jointly contributes to bipolar disorder and endometriosis, and their apparent comorbidity, in women. Second, I propose and test the hypothesis that endometriosis and polycystic ovary syndrome (PCOS) are diametric disorders of female hypothalamic-pituitary-gonadal axis development and functioning, with risk strongly mediated by opposite and extreme levels of testosterone. Diverse lines of evidence from endocrinology, developmental biology, epidemiology, reproductive physiology, and morphology confirm that endometriosis and PCOS involve opposite risk factors, symptoms, and correlates. Third, I collect and analyze data from women with endometriosis or PCOS to examine cognitive empathy ability in relationship to reproductive disorder status, pain levels, and medication usage. Finally, I shift my focus from disease to health, investigating the role of oxytocin-mediated interrelationships among coitus, birth, and lactation in the tradition of the late biologist, Niles Newton, to provide insights into women's capacity for extensive sexual pleasure. These findings offer a novel and unifying explanation of the causes of endometriosis, as well as a fresh and generative perspective concerning the origins and functions of female orgasm - and sexual pleasure - more broadly. Exploring how evolutionary dynamics shape interconnected psychological and physiological aspects of female reproduction increases our understanding of women's vulnerability to disease as well as women's capacity for health and wellbeing.

Keywords: oxytocin; testosterone; endometriosis; polycystic ovary syndrome (PCOS); bipolar disorder; orgasm; parturition; anogenital distance (AGD); empathy; hypothalamic-pituitary-gonadal (HPG) axis

Dedication

This body of work is dedicated to human females everywhere - girls, women, mothers, sisters, allomothers, grandmothers, aunts, and daughters. May we embody and be guided by the Great Mother, always.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

2D4D	Second to fourth digit ratio
BCE	Before common era
BDI	Beck's Depression Inventory
BMI	Body mass index
AGD	Anogenital distance
AMH	Anti-Müllerian hormone
DSM	Diagnostic statistical manual
E2	Estradiol
ESR	Expanded sexual response
FSFI	Female Sexual Function Index
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
HPG	Hypothalamic-pituitary-gonadal
IUD	Intrauterine device
IVF	*in vitro* fertilization
LH	Luteinizing hormone
NAc	Nucleus accumbens
NO	Nitrous oxide
OT	Oxytocin
OXT	Gene encoding oxytocin
OXTR	Gene encoding oxytocin receptor
PCOS	Polycystic ovary syndrome
RMET	Reading the Mind in the Eyes test
SHBG	Sex hormone binding globulin
T	Testosterone
VTA	Ventral tegmental area
WHR	Waist to hip ratio

Chapter 1. Introduction

Evolutionary processes shape our species' risk of disease as well as our capacity for health. Selection favours traits and behaviours that confer survival or reproductive benefits, even if such phenotypes reduce health, happiness, and longevity (Gluckman et al., 2011). For female mammals, including human females, the struggle to reproduce broadly involves participation in diverse social relationships, sexual intercourse, parturition, lactation, and mothering of vulnerable offspring. These different aspects and phases of female reproductive life, orchestrated by intricate, condition- and context-dependent endocrine mechanisms, involve significant risk and energy expenditure and are reinforced with intense emotions (Roney, 2016). Novel or highly elaborated reproductive features in the human lineage, such as copious menstruation, invasive placentation, social cognition, and cooperative breeding generate increased scope for trait dysfunction and disease, but also appear to grant unique capacities (Crespi, 2010; Hrdy, 2009; Levin; 2017). The body of work below explores how evolutionary dynamics shape interconnected psychological and physiological aspects of women's reproduction, creating patterns of disease risk as well as potentials for pleasure.

The field of evolutionary medicine applies principles of biological evolution to understand, categorize, diagnose, and treat disease (Stearns, 2012). Indeed, our minds, bodies, and behaviours represent 'bundles of compromises' in that selection is constrained in its ability to sculpt perfect solutions to the plethora of adaptive problems vying for time, energy, and resources. Evolutionary medicine unifies disparate findings from medicine, psychiatry, physiology, and endocrinology, illuminating why particular traits and systems of the human mind and body are sensitive to dysregulation in different environments. Fundamental concepts from evolutionary biology, such as pleiotropy and tradeoffs, provide insights into the way that groups of symptoms, risk factors, and diseases cluster together within individuals (Crespi, 2010).

Pleiotropy, the phenomenon of one gene with many effects, shapes disease risk in diverse ways (Paaby & Rockman, 2013). For example, antagonistic pleiotropy occurs when selected alleles confer positive effects in one context, system, or phase of life, but negative effects in another context; diseases of aging frequently involve this process (Crespi, 2010). Alternatively, a pleiotropic system that adaptively coordinates multiple

beneficial traits may be sensitive to dysregulation when environmental or genetic factors significantly increase or decrease its level of activity. Such dysregulation can then manifest as syndromes or multiple diseases exhibiting comorbidity within individuals, due to the influence of the pleiotropic system on the development and expression of diverse traits and processes (Crespi; 2010; Paaby & Rockman, 2013).

Oxytocin is a paradigmatic example of a pleiotropic system with a central role in female reproduction. Produced in the hypothalamus and secreted in pulses from the posterior pituitary, the neurohormone oxytocin evolved alongside viviparity, placentation, lactation, and extended maternal care (Carter, 2014; Crespi, 2016). Large quantities of oxytocin are centrally released during coitus, birth, and lactation, and participation in these intimate reproductive partnerships elicits care-taking behaviour and bonding (Newton, 1992). The empathic and relational functions of oxytocin, as well as its broad parasympathetic effects, are widely characterized. Less appreciated is that oxytocin also influences diverse aspects of female reproductive physiology, such as luteal degradation and uterine contractility; these impact a woman's ability to become and remain pregnant, as well as to give birth at the optimal time (Carter, 1992; Saller et al., 2010; Bishop, 2013).

Through its interactions with gonadal hormones like estrogen and testosterone, and neurotransmitters like dopamine and opioids, oxytocin coordinates female psychology and behaviour with reproductive physiology (Roney, 2016). For example, peaks in estrogen prior to ovulation coincide with rising oxytocin levels and together, this interaction appears to coordinate approach behaviour and sexual receptivity with oxytocin-mediated sperm transport during the fertile phase of a woman's cycle (Salonia et al., 2005; Kunz et al., 2007). The pleiotropic oxytocin system thus affects women's psychological, relational, and reproductive functioning, impacting disease risk as well as health and wellbeing. In Chapter 2, I investigate how elevated activity of the oxytocinergic system jointly contributes to uterine dysfunction and mood disorder in women. In Chapter 5, I explore how oxytocin's regulation of the nervous system during participation in the reproductive partnerships of sex, birth, and lactation shapes women's capacity for pleasure.

A particularly generative framework within evolutionary medicine is diametric disorders (Crespi & Go, 2015). The diametric disorders framework draws on the basic

truth that biological systems can vary in two directions, toward relatively reduced or elevated activity. For example, gene expression, neurotransmitter production, and hormonal secretion can increase or decrease, maturation can occur earlier or later, and growth can happen quickly or slowly. A shift toward relatively lower or higher expression or activity of a given trait or process will impose costs or benefits in other traits or processes, as metabolic energy and time required for trait development and expression are limited resources (Crespi & Go, 2015). Such pervasiveness of tradeoffs in biological systems engender adaptive compromises and high levels of individual variation, as different quantities of trait expression and system activity can result in equivalent levels of fitness across individuals.

Another key component of the diametric disorders framework is that probability of dysfunction in a given trait or system increases at the opposite and extreme ends of trait expression or system activity. Thus, diseases of the same biological system will manifest as pairs of disorders where one occurs as a consequence of very low system activity and the other occurs as a consequence of very high system activity. Such a disease pair will demonstrate diametrically opposed risk factors, proximate causes, symptoms, treatments, and comorbidities (Crespi & Go, 2015). An illustrative example is the immune system: both naturally occurring variation and environmental perturbations generate a spectrum of immune response that can range from very low to extremely high. When immune activity is low, infectious disease risk increases, and by contrast, when immune activity is high, autoimmunity risk increases. The diametric disorders framework is useful because knowledge of one disorder instantly provides insights into the other paired disorder. Further, identifying and describing pairs of diseases through this framework can illuminate the selective pressures and tradeoffs that shape axes of variation in biological systems. In Chapter 3, I draw on the diametric disorders framework to develop and investigate the hypothesis that two commonly occurring reproductive diseases involve opposite alterations to the development and activity of the female hypothalamic-pituitary-gonadal (HPG) axis. Some predictions stemming from this hypothesis are tested with self-reported psychological and diagnostic data in Chapter 4.

Studies of women's diseases compared to men's diseases have historically received less research attention and funding (Mirin, 2021). Biases, including the treatment of women as smaller men, or the exclusion of women in clinical research due to the complexity of ovulatory cycles, have negatively impacted knowledge of female

health (Morselli et al., 2016). Some biases, such as androcentrism, where a trait in males is held as the standard against which female traits are compared, extend to studies of female reproductive biology more broadly (Lloyd, 2005). There is also a tendency to focus on female dysfunction to such an extent that some capacities of women, such as expanded sexual response (ESR; Sayin, 2011), are barely acknowledged. Though evolutionary biology is often perceived as irreconcilable with the aims of feminism, there now exist scholars and perspectives merging the two approaches (e.g. Fisher et al., 2013). Recognizing and understanding the ways that evolution has shaped women's biology can usefully inform healthcare as well as public policy. In the current cultural milieu, there is resistance to acknowledging evolved sex differences, especially those female reproductive processes that have historically increased women's vulnerability to neglect, abuse, and stigma. One approach to merging feminism with biology involves separating reproductive processes from mental and cognitive processes, perhaps as an attempt to reject earlier attitudes that framed females as less intelligent *because* of their reproductive capacities. I suggest that a more productive way forward is to clearly demonstrate how evolutionary processes, especially the struggle to reproduce, shapes mechanisms that weave together women's mind, bodies, and behaviours: such an approach is empirically and theoretically grounded.

Through drawing on principles of evolutionary theory and evolutionary medicine, the body of work below investigates the polarities and extremes, the pleasures and pains, of the human female. In Chapter 1, I review existing literature to investigate the hypothesis that elevated activity of the oxytocin system explains epidemiological associations between bipolar disorder and endometriosis. Next, in Chapter 2, I evaluate the hypothesis that endometriosis and polycystic ovary syndrome (PCOS) are diametric disorders with opposite risk factors, causes, and symptoms through synthesizing literature from endocrinology, developmental biology, epidemiology, reproductive physiology, and morphology. In Chapter 3, I collect new data from women with endometriosis or PCOS to test some of the predictions from the first two chapters, specifically, do women with endometriosis exhibit elevated skill on a mind-reading task relative to unaffected women and women with PCOS? In Chapter 4, I shift my focus from women's disease to women's health, examining how oxytocin-mediated interrelationships among sex, birth, and breastfeeding provide insights into the longstanding debate concerning female orgasm and its proposed functions.

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Chapter 2. Revisiting the Wandering Womb: Oxytocin in Endometriosis and Bipolar Disorder

Natalie L. Dinsdale & Bernard J. Crespi

2.1. Abstract

Hippocrates attributed women's high emotionality – hysteria - to a 'wandering womb'. Although hysteria diagnoses were abandoned along with the notion that displaced wombs cause emotional disturbance, recent research suggests that elevated levels of oxytocin occur in both bipolar disorder and endometriosis, a gynecological condition involving migration of endometrial tissue beyond the uterus. We propose and evaluate the hypothesis that elevated oxytocinergic system activity jointly contributes to bipolar disorder and endometriosis. First, we provide relevant background on endometriosis and bipolar disorder, and then we examine evidence for comorbidity between these conditions. We next: (1) review oxytocin's associations with personality traits, especially extraversion and openness, and how they overlap with bipolar spectrum traits; (2) describe evidence for higher oxytocinergic activity in both endometriosis and bipolar disorder; (3) examine altered hypothalamic-pituitary-gonadal axis functioning in both conditions; (4) describe data showing that medications that treat one condition can improve symptoms of the other; (5) discuss fitness-related impacts of endometriosis and bipolar disorder; and (6) review a pair of conditions, polycystic ovary syndrome and autism, that show evidence of involving reduced oxytocinergic activity, in direct contrast to endometriosis and bipolar disorder. Considered together, the bipolar spectrum and endometriosis appear to involve dysregulated high extremes of normally adaptive pleiotropy in the female oxytocin system, whereby elevated levels of oxytocinergic activity coordinate outgoing sociality with heightened fertility, apparently characterizing, overall, a faster life history. These findings should prompt a re-examination of how mind-body interactions, and the pleiotropic endocrine systems that underlie them, contribute to health and disease.

2.2. Introduction

Egyptian medical records dating back to 1990 BCE describe cases of women experiencing erratic emotions with accompanying physical manifestations including seizures, paralysis, choking, and mutism (Novais et al., 2015). Because of their female specificity, medical and gynecological practitioners and writers of antiquity such as Aretaeus, Soranus, Plato, Hippocrates, and Galen explained these symptoms as emerging from the womb (Novais et al., 2015; Tasca et al., 2012; Gilman et al., 1993). A belief held by some of these men was that the womb was a separate being or even an animalistic entity that lived within a woman and could cause health issues by wandering around her body and disturbing other organs (reviewed in Gilman et al., 1993). Hippocrates (460 – 377 BCE) grouped these heterogeneous symptoms under *hysteria* (from Greek *hysterikos,* meaning 'of the womb'), a term that has since been subsumed into other diagnostic labels (Figure 2.1). Debate over the nature of the womb and its ability to truly wander around a woman's body continued well into the Renaissance, informing medical treatments and influencing attitudes about women (Novais et al., 2015).

In a continuation of ascribing animalistic traits to women, the 'father of psychiatry,' Emil Kraepelin, characterized hysteria as a clash between instinct and volition, intuiting later psychoanalytic developments that emphasized the role of conflicting drives in hysteria, and psychopathology more generally (Decker, 2004). Within the frameworks of the DSM, the dissociative and somatic symptoms formerly belonging to hysteria remain, and are commonly observed in mood and personality disorders, including bipolar disorder (Figure 2.1). Although severe forms of bipolar disorder are equally prevalent in both sexes (Blanco et al., 2017), women tend to report higher levels of somatic, dissociative and mood symptoms (Delisle et al., 2012; Dessotte et al., 2015; Tabassum & Farooq, 2007), and overall, meet criteria for affective disorders much more frequently than men (O'Donnell et al., 2016).

Bipolar disorder, characterized by alternating high and low affective states, is different from hysteria, but it has long been recognized that the two phenotypes overlap, especially with respect to mood volatility (noted by Kraepelin; reviewed in Kapfhammer, 2001). Somatic symptoms, such as muscular tension and migraines, are frequently observed in people seeking treatment for bipolar disorder (Tavormina, 2011). For about

half of women with bipolar disorder, shifts in menstrual cycle phase also precede symptom onset, and menstrual cycling notably impacts symptom severity (Teatero et al., 2014), highlighting the complex interplay between the body, particularly with respect to female reproductive physiology, and psychological health (Galea et al., 2016).

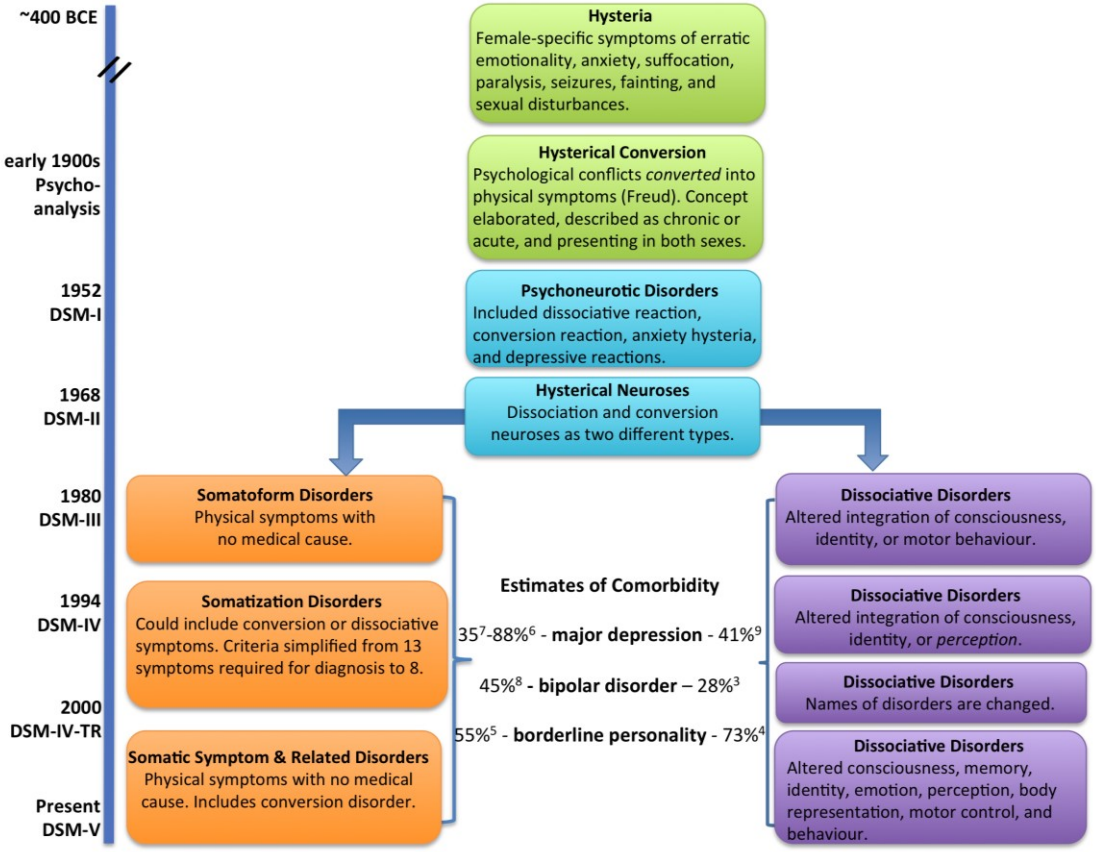
The interactions of mind with body - and their joint disturbance in female-preponderant psychiatric diagnoses - thus centrally contributed to the emergence of psychiatry, and at present remain both mysterious and difficult to study and treat. Such difficulties apparently derive in part from sharp demarcation of medicine (for the body) from psychology (for the mind) and more broadly, they represent an outcome of persistent dualistic concepts of ‘mind’ and ‘body’, which constrain our abilities to accurately perceive and communicate about mind-body interactions (Van Oudenhove & Cuypers, 2010).

Although a ‘wandering womb’ was long ago dismissed as causing mental illness, recent evidence links oxytocin, a neuropeptide that mediates both uterine contractility and social bonding, with diverse and correlated psychological and physical symptoms and conditions that more frequently affect women than men (Seng, 2010). In this article, we propose the novel hypothesis that elevated oxytocin activity, via some combination of increased serum oxytocin and increased expression and densities of oxytocin receptors, jointly mediates risk of bipolar disorder and endometriosis in women (Figure 2.2).

To evaluate this hypothesis, we draw on multiple lines of evidence. We begin by describing salient aspects of the oxytocinergic system, and provide relevant background information on the symptoms and causes of endometriosis and bipolar disorder. We then describe and evaluate evidence of comorbidity between these two disorders and investigate evidence regarding its causes. These lines of salient evidence include: (1) oxytocin’s influence on personality traits, especially extraversion and openness; (2) higher oxytocinergic activity in both endometriosis and bipolar disorder; (3) abnormal hypothalamic-pituitary-gonadal (HPG) axis functioning in both conditions, including overlapping patterns of menstrual characteristics; (4) the presence of a set of medications commonly used to treat bipolar disorder that appear to improve endometriosis symptoms, and vice versa; (5) observed, and hypothesized, fitness-related impacts of endometriosis and bipolar disorder as well as their non-clinical, less-severe phenotypes; and (6) a pair of correlated reproductive and psychological

disorders, polycystic ovary syndrome and autism, that appear to involve reduced oxytocinergic activity, thus representing an 'opposite' pair of conditions to endometriosis and bipolar disorder.

Figure 2.1 Simplified timeline[1, 2] and comorbidities[3-9] of hysteria-related, female-preponderant categories. Hysteria is no longer a diagnostic category but its heterogeneous symptoms still exist and have been subsumed by other diagnoses in modern versions of the DSM.



References: 1) North 2015; 2) Kapfhammer 2001; 3) Yayla et al 2014; 4) Sar et al 2006; 5) Rechlin et al 1997; 6) Bowman & Markand 1996; 7) Kuloglu et al 2003; 8) Tavormina 2011; 9) Sar et al 2013

Finally, we explore the extent to which high oxytocin levels adaptively coordinate psychological and physiological traits within women, possibly contributing to a faster life history strategy that is characterized by a combination of high sociality and early, high fertility. Although the ‘wandering womb’ is now considered a historical anecdote, the proposed hypothesis highlights its apparent essential truth: uterine activity and psychological health are indeed linked, via complex and oxytocin-dependent effects.

2.2.1. Oxytocin, Sociality, and Physiology

The neuropeptide oxytocin emerged in concert with placentation, viviparity, lactation, and extended maternal care among mammals, and is well known for its role in regulating maternal-offspring interactions and sociality much more broadly (Crespi, 2016; Feldman, 2016). One of oxytocin's most conserved functions is the contraction of smooth muscles, notably of the uterus during parturition, which inspired its name, as oxytocin means '*quick birth'* in Greek (H. Lee et al., 2009).

In addition to its modulation of reproductive processes and social behaviour, oxytocin also mediates immune functioning and wound healing (Elabd et al., 2014; Gouin et al., 2010; Li et al., 2017), cardiovascular activity (Gutkowska et al., 2014), and energy homeostasis and stress-responsiveness (Smith et al., 2015). These diverse effects are exerted through oxytocin's central release from magnocellular neurons in the neurohypophysis and its subsequent entrance into general circulation, as well as through its peripheral production in, and action upon, multiple tissues including the heart, ovaries, and uterus (Gimpl et al., 2001). Overall, oxytocin is a highly abundant chemical messenger in both the brain and the body, acting as a neurotransmitter that alters brain connectivity for extended periods of time, and as a hormone that coordinates physiological processes with behavioural states (Bethlehem et al., 2013; Gimpl et al., 2001).

A large body of research reveals that oxytocin augments prosocial behaviour such as empathy, trust, and maternal sensitivity, through both endogenous release and artificial administration (Striepens et al., 2011). Although oxytocin's effects vary widely depending on contextual and individual factors (Bartz et al., 2011), the majority of studies tend to focus on oxytocin's positive impacts on psychological and social functioning. However, a recent and comprehensive review demonstrates that elevated oxytocin levels can also predict aspects of negative emotionality, including increased interpersonal distress, relationship anxiety, and sustained attention to stressful social situations, especially in women (Crespi, 2016; Grebe et al., 2017). These findings indicate that elevated oxytocin levels can mediate either prosociality or social and relational vulnerability, motivating an individual to attend to and process social information salient to navigating complex and valuable relationships.

Aspects of social cognition and mentalizing tend to be elevated and exaggerated in psychological disorders that belong to the psychotic-affective spectrum, and several of these conditions, including schizophrenia, bipolar disorder, and depression, show associations with increased levels of oxytocin in some studies (Crespi, 2016). Oxytocin is also elevated in women with post-traumatic stress disorder, and positively correlated with dissociative symptoms as well as physical symptoms including severe nausea and vomiting during pregnancy (Seng et al., 2013). Although the detrimental effects of low oxytocin levels in psychiatric conditions are relatively well characterized (Cochran et al., 2013), the contribution of *high* levels of oxytocin to psychiatric - and physical – disease remains almost entirely underexplored.

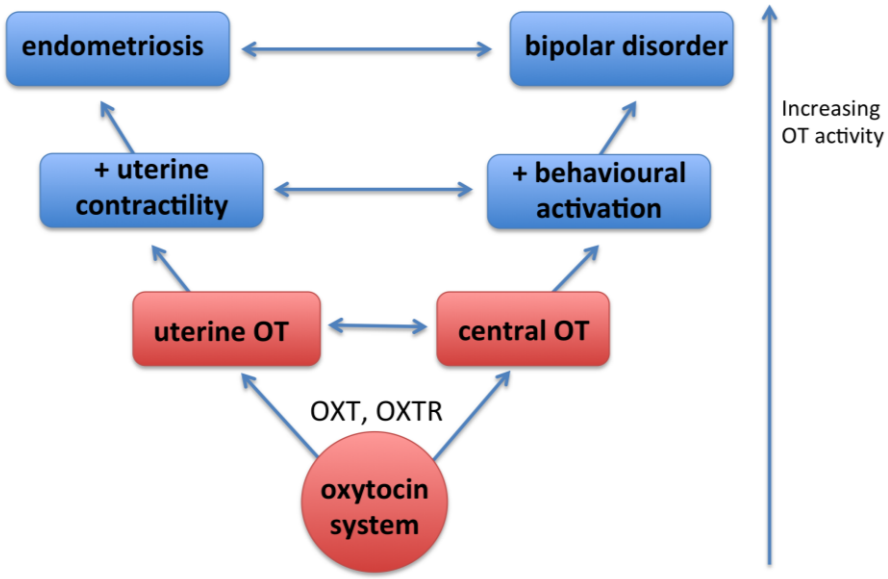
Large quantities of oxytocin are centrally released during coitus, parturition, and suckling, revealing oxytocin's key roles in coordinating interpersonal and reproductive functions (Gimpl et al., 2001; Roney, 2016). The uterus becomes increasingly sensitive to oxytocin in late pregnancy and locally produced oxytocin may play a role in regulating the onset of labour (Kimura et al., 2013). Levels of oxytocin fluctuate with women's menstrual cycles; rising oxytocin levels coincide with peaks in estrogen prior to ovulation, coordinating sexual receptivity with oxytocin-mediated sperm transport during the fertile phase of a woman's cycle (Kunz et al., 2007; Salonia et al., 2005). Oxytocin influences other, diverse aspects of female reproductive physiology, such as luteal degradation, uterine contractility, and embryo positioning; these roles are not fully understood in humans but plausibly impact a woman's ability to become and remain pregnant, as well as to give birth at an optimal time (Bishop, 2013; Carter, 1992; Furuya et al., 1995; Saller et al., 2010).

Oxytocin is produced and its effects are exerted through the action of two genes: one gene encodes oxytocin and its precursor (oxytocin-neurophysin I; OXT), and another gene encodes oxytocin's singular receptor (the oxytocin receptor; OXTR). Because OXT and OXTR gene products each influence a diverse range of phenotypes, the oxytocin system is highly pleiotropic (Paaby & Rockman, 2013), in that changes to either or both of these genes will impact not only social behaviour, but numerous physiological processes as well. Such pleiotropy is indeed central to oxytocin's evolved functions as a neuropeptide that, among mammals, is the primary hormone for coordinating physiological processes with behavioural aspects of viviparity and maternal care (Crespi, 2016). As such, high oxytocinergic activity in the physiological domain is

expected to coincide with high activity in oxytocin-mediated cognitive and behavioural domains, and conversely for low activity in both.

Generally, biological systems can be altered toward greater or reduced activity, and an evolutionary framework for health and disease suggests that diseases, as forms of maladaptation, often represent extremes of adaptive phenotypes in either of these two directions (Crespi & Go, 2015). Elevated activity of the oxytocin system may thus, through its pleiotropic nature, be expected to jointly contribute to psychological and physiological symptoms and diseases. Thus, as described in more detail below, in endometriosis heightened oxytocinergic activity appears to increase uterine muscle contractility to an extent that fertility is disrupted, and for bipolar disorder, heightened oxytocinergic activity may increase social approach tendencies to an extent that disturbs healthy goal-seeking behaviour and mood (Figure 2.2).

Figure 2.2 Hypothesized effects of elevated oxytocin system activity on psychological and physiological traits that contribute to bipolar disorder and endometriosis



A highly simplified diagram showing how the pleiotropic genes (OXT, OXTR) that shape the oxytocin (OT) system contribute to both uterine and central OT levels and OT receptor densities. Given OT's potentiating effects on uterine contractility and social behaviour, it is hypothesized that as net OT system activity increases, through either increased OT levels or heightened OT receptor densities or both, the joint risk of endometriosis and bipolar disorder also increases. Under this model, OT-mediated physiological and psychological processes are positively associated, and jointly affected by increasing (or decreasing) oxytocin system activity.

2.2.2. Endometriosis and Adenomyosis

Two reproductive disorders centrally involve the displacement of endometrial tissue from its native position. Endometriosis is an estrogen-dependent disease that involves the migration and proliferation of endometrial glands and stroma into the ovaries, fallopian tubes (oviducts), and peritoneal cavity (Leyendecker et al., 2009). A contributor to female infertility, endometriosis causes pain in up to 80% of affected women, while up to one quarter are asymptomatic (Bulletti et al., 2010). Endometriosis ranges in severity with respect to the intensity and chronicity of pain experienced, as well with the depth and invasiveness of lesions (Koninckx et al., 2016). Adenomyosis is diagnosed when cells of the endometrial lining grow within the uterine muscle cells that comprise the uterine wall (the myometrium); as the myometrium enlarges, painful menstruation occurs (Vercellini et al., 2006). Affecting approximately 10-18% of women, adenomyosis prevalence is difficult to assess because of differences in diagnostic criteria (Vercellini et al., 2006). Endometriosis occurs in about 80-90% of women with adenomyosis, and both diagnoses are heritable with approximately half of the variation in risk due to genetic factors (Kissler et al., 2007; Saha et al., 2015).

The etiologies of endometriosis and adenomyosis are not fully understood, but the conditions do involve some well-characterized alterations to normal reproductive physiological processes, including hormonally regulated uterine motion (Leyendecker et al., 2004). All non-pregnant uteri are constantly in motion, but endometriosis and adenomyosis uteri express very intense patterns of contraction, which cause excess strain on tissues that elicits constant repair (Kobayashi et al., 2013; Leyendecker et al., 2009). Tissue repair, plus the cyclical growth and shedding of the endometrium, requires a balance between cellular proliferation and apoptosis; this balance is dysregulated in endometriosis uteri, resulting in a state of chronic inflammation that is maintained by estrogen production in endometriosis lesions (Kobayashi et al., 2013; Leyendecker et al., 2009). Indeed, multiple indicators of chronic inflammation, such as immune cells in the peritoneal fluid and elevated levels of prostaglandins and cytokines, are observed in women with endometriosis (Kobayashi et al., 2013). Uterine motion also creates retrograde menstruation, the backward and upward movement of menstrual secretions, which occurs in most women, but for reasons not fully understood, develops into endometrial lesions in a subset (Leyendecker et al., 2004). It is plausible that vascular and lymphatic dissemination of menstrual secretions could also be mediated and

facilitated by enhanced myometrial contractility. Elevated contractility of the uterus thus contributes to the primary phenomenon of endometriosis and adenomyosis (Kunz et al., 2007; Leyendecker et al., 1996).

2.2.3. Bipolar Disorder

Bipolar disorder is characterized by alternating periods of depression and mania or hypomania, but high levels of heterogeneity in both the duration and severity of mood fluctuations have prompted the usage of multiple labels within this broader diagnostic category (DSM-V; APA, 2013). For example, bipolar I disorder is the most chronic and severe form, involving both manic and depressive episodes that usually begin in the second decade of life; lifetime prevalence of bipolar I disorder is around 1-2% and does not differ between the sexes (Blanco et al., 2017). Other forms of bipolar disorder include cyclothymic disorder, a relatively mild diagnosis that involves depressive and hypomanic symptoms, and bipolar II disorder, characterized by major depressive and hypomanic episodes (Angst et al., 2003). These less severe manifestations of bipolar disorder tend be more prevalent in women (S. Lee et al., 2009; Merikangas et al., 2011), although some studies do not find a sex difference (Dell'Aglio et al., 2013). Bipolar traits and symptoms also occur in healthy people, indicating that bipolar disorder is most accurately conceptualized as a spectrum with manifestations in both clinical and non-clinical populations (Dell'Aglio et al., 2013).

For all bipolar disorders, the defining characteristic is mania, or its less extreme form, hypomania, which involve elevated mood and hyperactivity that ranges from elation and risk-taking to irritability and recklessness (DSM-V; APA, 2013). Mania is heterogeneous, involving combinations of grandiosity, racing thoughts, rapid speech, distractibility, increased goal-directed activity, agitation, risky behaviour, and altered sleep patterns (DSM-V; APA, 2013). These multiple features observed in manic episodes can be generally understood as involving behavioural and psychomotor activation and goal-seeking (Johnson et al., 2012; Scott et al., 2017).

Bipolar symptoms in women fluctuate with the menstrual cycle and both manic and depressive symptoms can be initiated by ovulatory or premenstrual phases (Teatero et al., 2014). Childbirth constitutes a high-risk period for the onset of hypomania in women with major depression, due in part to low estrogen levels following parturition,

and women with postpartum psychotic symptoms respond well to estrogen supplementation (Meinhard et al., 2014; Sharma et al., 2014). Estrogen appears to exert its effects on bipolar symptoms through modulating neurotransmitter systems and intracellular signaling pathways (Frey & Dias, 2014.) Although fluctuating estrogen impacts bipolar symptoms, individual heterogeneity is high, and women with and without bipolar disorder tend to show equivalent levels of estrogen (Teatero et al., 2014). For women, bipolar disorder is thus closely linked to the reproductive cycle, though the relationship is not fully understood.

2.2.4. Comorbidity of Endometriosis with Bipolar Disorder

Women with endometriosis manifest heightened vulnerability to certain psychiatric disorders, especially the tendency toward anxiety and depression, though these relationships interact with level and chronicity of pain in complex ways so it is essential that studies include measures of pain levels or pain-matched control groups (reviewed in Pope et al., 2015). In Pope and colleagues' (2015) meta-analysis, major depression occurred more frequently in the non-endometriosis control group (36.4% compared to 18%) while bipolar disorder was more prevalent in the endometriosis group (16.7% compared to 2.7%). Similarly, Ferrero and colleagues (2006) found that panic and somatoform disorders were significantly more frequent in women with endometriosis than in unaffected women; panic and somatoform disorders belong to the larger diagnostic category of somatization, which is highly comorbid with bipolar disorder (Figure 2.1).

This apparent comorbidity between endometriosis and bipolar disorder has been specifically examined in four studies, with mixed results. Lewis and colleagues (1987) first documented comorbidity between the two conditions, reporting that 62.5% of endometriosis patients from a small sample (n = 16) drawn from a university clinic met bipolar criteria or had already been diagnosed, while only 12% met criteria for major depression. Furthermore, 56% of the endometriosis patients reported having a first-degree relative with a mood disorder. The lack of control or comparison group in Lewis and colleagues' study however makes it difficult to assess the specificity of the bipolar-endometriosis link. A subsequent attempt to replicate these findings (Walker et al., 1989) included a control group, but failed to find evidence for either increased prevalence of bipolar disorder, or for higher rates of first-degree relatives with affective disorders, in

endometriosis patients. While the inclusion of control subjects (n = 55) strengthens these findings, the control group included women with and without pelvic pain, and the pain levels of subjects - including the endometriosis patients (n = 14) - were not assessed, rendering possible interactions between psychiatric features and pain unknown.

To expand upon these contradictory findings, Kumar and colleagues (2011) assessed the prevalence of bipolar disorder in women with endometriosis (n = 27) and women with pelvic pain but no endometriosis (n = 12). Importantly and in contrast to Walker and colleagues, Kumar's team assessed pain levels and found no group differences, so the results on bipolar prevalence cannot be attributed to pain. Bipolar disorder was significantly more prevalent in endometriosis patients than expected (8.3 expected, 12 actual; $\chi 2 = 7.96$, $p < 0.019$). In a recent study, Osório and colleagues (2016) found that women with chronic pelvic pain (n = 50) were more likely than pain-free women to meet criteria for mood disorders, including bipolar disorder and major depression. However, Osório and colleagues did not find evidence for increased prevalence of bipolar disorder among a subgroup of women with endometriosis (n = 24), though the control group against which they compared bipolar prevalence (endometriosis versus pelvic pain, endometriosis versus no pelvic pain, or both) was not mentioned.

Patterns of comorbidity can be further examined by assessing personality traits in women with endometriosis, as some women may not meet psychiatric diagnostic thresholds but might manifest elevated levels of certain personality traits that tend to predict increased susceptibility to psychiatric disorders. Low and colleagues (1993) reported elevated levels of psychoticism, introversion, and anxiety in women with endometriosis compared to women with matched levels of pelvic pain but no endometriosis. Psychotic features and symptoms do overlap with the bipolar spectrum, affecting approximately half of people with a bipolar diagnosis (Özyildirim et al., 2010); increased psychoticism in women with endometriosis is consistent with a link to bipolar disorder. In contrast, Cavaggioni and colleagues (2014) did not find differences in psychotic, or somatic, symptoms between endometriosis patients and control subjects, but women with endometriosis showed significantly higher levels of obsessive-compulsive and depressive traits. Facchin and colleagues (2016) measured novelty-seeking and self-transcendence in women with endometriosis, two traits which are uniquely elevated in bipolar disorder relative to major depressive disorder (Zaninotto et

al., 2016). Because Facchin and colleagues (2016) were interested in the relationship between pain and personality in women with endometriosis, they measured but did not compare or discuss personality differences between women with pain-free endometriosis and healthy pain-free subjects. Comparing these two groups can reveal personality traits unique to endometriosis without the confounding influence of pain.

We analyzed Facchin and colleagues' (2016) published data to examine whether or not bipolar spectrum traits were associated with endometriosis. For the dimension of novelty-seeking, total scores did not significantly differ between unaffected women and women with pain-free endometriosis; however, impulsiveness, a subscale of novelty-seeking, was higher in women with pain-free endometriosis (n = 24, $\bar{x}$ = 25.9) relative to unaffected women (n = 51, $\bar{x}$ = 24.1) at a trend level of significance (t = 1.34, p = 0.09). Mean self-transcendence scores were four points higher in women with pain-free endometriosis ($\bar{x}$ = 72.2) than unaffected women ($\bar{x}$ = 68.1) but this difference was not significant (t = 1.19, p = 0.12). However, scores on transpersonal identification, a subscale of self-transcendence that refers to a sense of unity with objects beyond the self (Cloninger et al., 1993), were elevated in women with pain-free endometriosis ($\bar{x}$ = 21.4) relative to healthy controls ($\bar{x}$ = 19.4), at a trend level of significance (t = 1.41, p = 0.08). These data support the view that women with endometriosis express elevated levels of some bipolar spectrum traits.

Research examining the relationship between endometriosis and bipolar disorder is summarized in Table 2.1 and is notably suggestive of comorbidity between the two conditions. Personality traits of women with endometriosis appear to differ from unaffected women, and some of these differences are unique to the bipolar spectrum. Given that two of four studies found increased prevalence of bipolar disorder in endometriosis (Kumar et al., 2011; Lewis et al., 1987), and that one of these studies controlled for pain levels (Kumar et al., 2011), and that across multiple studies, bipolar disorder - but not major depression - appears more frequently in women with endometriosis relative to unaffected women (Pope et al., 2015), the connection between these two conditions is, we believe, sufficiently compelling to warrant further examination.

Table 2.1 Summary of findings from studies investigating personality and mental illness in women with endometriosis

Author	Year	Method	Key Finding
Lewis et al	1987	Clinical sample with no control group	High rates of bipolar disorder in women with endometriosis
Walker et al	1989	Study included control group but did not measure or match pain levels	No difference in rates of bipolar disorder in women with or without endometriosis
Low et al	1993	Study included control group and matched for pain levels	Elevated psychoticism, introversion, and anxiety in women with endometriosis
Ferrero et al	2006	Study with control group and measures of pain levels	Increased rates of panic and somatoform disorders in women with endometriosis
Kumar et al	2011	Study with control group and matched for pain levels	Bipolar disorder more prevalent in women with endometriosis than expected
Cavaggioni et al	2014	Study with control group and measures for pain levels	Elevated levels of obsessive-compulsive and depressive traits in women with endometriosis
Pope et al	2015	Meta-analysis	Increased rates of bipolar disorder in women with endometriosis
Facchin et al	2016	Study with control group and measures of pain levels	Trend of higher levels of bipolar spectrum traits, including impulsiveness and spiritual experiences, in women with endometriosis

2.3. Review of Evidence

2.3.1. Oxytocin, Personality Traits, and Psychiatric Diagnoses

Oxytocin promotes social behaviour and bonding through affective and cognitive pathways. The release or administration of oxytocin can reduce fear and anxiety via attenuation of amygdala activity, as well as enhancing attention to and processing of socially salient stimuli (Domes et al., 2007; MacDonald & MacDonald, 2010; Shamay-Tsoory & Abu-Akel, 2016). Oxytocinergic neurons in the hypothalamus project to the ventral tegmental area (VTA), a key region of the reward pathway rich in both dopaminergic neurons and oxytocin receptors, as well as to the nucleus accumbens (NAc), amygdala, hippocampus, and prefrontal cortex, all of which also receive

projections from dopaminergic neurons (Skuse & Gallagher, 2009). These complex oxytocin-dopamine interactions imbue social stimuli with reward and facilitate approach-avoidance behaviours (Love, 2014), promoting long-term memory formation, social recognition, and behavioural synchrony; together, these processes support bonding across interpersonal contexts such as mother-offspring, mating, and friendship (Feldman, 2016). Together, the anxiolytic, stress-reducing, and rewarding properties of oxytocin release can function to reduce the threshold for social approach behaviours (Kemp & Guastella, 2011), though these prosocial effects depend on contextual and individual factors such as familiarity and attachment (Bartz et al., 2011).

Oxytocin's modulation of social approach tendencies is evident through its relationship to specific personality dimensions, especially extraversion, openness, and creativity. Extraversion is a relatively stable personality trait that encompasses facets of warmth, positive affect, gregariousness, and responsiveness to reward, while openness to experience reflects intellectual curiosity and imagination (Power & Pluess, 2015).

Andari and colleagues (2014) reported that levels of plasma oxytocin positively predict self-reported ratings of extraversion, and together, plasma oxytocin levels and extraversion scores negatively predict volumes of the amygdala and hippocampus, brain regions important in fear processing and memory consolidation. Interestingly, oxytocin administration also influences beliefs about one's social behaviour: Cardoso and colleagues (2012) found that people self-reported higher levels of extraversion and openness to experience if they had received oxytocin relative to a placebo. In a recent review, De Dreu and colleagues (2015) also proposed that the oxytocin system underlies creativity through its engagement of divergent and flexible cognitive pathways. Oxytocin, through interacting with dopamine-mediated neural pathways, thus shows evidence of contributing to extraversion, openness, and creativity.

Psychological disorders are increasingly considered as reflecting extremes of normally adaptive psychological and personality traits (Widiger & Trull, 2007). Mania, as the defining feature of bipolar disorder, may thus be conceptualized as reflecting high extremes of extraversion, openness, and creativity, in the general context of seeking fitness-related goals in one's environment. Both extraversion and mania involve reduced thresholds for behavioural approach, such as increased sexual activity (Kopeykina et al., 2016; Raynor & Levine, 2009), impulsivity and sensation-seeking (Strakowski et al.,

2010; Zuckerman & Glicksohn, 2016), and elevated creativity (Ma, 2009; McCraw et al., 2013). In numerous self-report studies using validated personality and diagnostic surveys, extraversion and openness positively predict levels of hypomanic personality traits such as energetic temperament, cheerfulness, irritability, and recklessness (Durbin et al., 2009; Meyer, 2002; Quilty et al., 2009). Approximately half of the variation in openness and extraversion can be attributed to genetic factors (Jang et al., 1996; Vernon et al., 2008), and genes underlying both traits also contribute to bipolar disorder risk. For example, Lo and colleagues (2017) reported significant, positive genetic correlations between extraversion and bipolar disorder (r = 0.18, p < 0.05) and openness and bipolar disorder (r = 0.34, p < 0.001). A novel model of personality found that both openness and extraversion were positively associated with a curious/energetic temperament, and the authors suggest that this temperament reflects the dopamine system, likely predisposing to mania as well as the broader psychotic-affective spectrum (Fisher et al., 2015).

Enhanced creativity is notably related to the bipolar spectrum (Greenwood, 2017; Taylor et al., 2015), among other psychotic-affective spectrum conditions (Nettle & Clegg, 2006), and mood disorders including bipolar tend to be more prevalent in families of artists and writers (Post, 1996). In a recent meta-analysis on personality dimensions in mood disorders, Zaninotto and colleagues (2016) reported that bipolar disorder was specifically predicted by elevated scores on measures of novelty-seeking, which includes impulsiveness and extravagance, as well as self-transcendence, which involves creativity and the tendency to experience a sense of unity or spirituality (Cloninger, 1993). The human capacity to have spiritual experiences is regulated in part by oxytocin (Crespi & Summers, 2014; Van Cappellen et al., 2016). These findings suggest that mania and the bipolar spectrum represent extreme variants of personality traits, including creativity, spirituality, openness, and extraversion, that are known from other work to be strongly mediated by oxytocin.

Consistent with the above patterns, people with bipolar disorder have been reported to exhibit heightened serum oxytocin levels. Turan and colleagues (2013) found that overall, oxytocin levels were higher in people with bipolar disorder than people without, and even after patients positively responded to treatment, serum oxytocin remained significantly elevated in patients. Oxytocin was highest in patients currently in a manic episode, and oxytocin levels in both remitted patients and currently-depressed

patients were significantly higher than non-patient levels. Similarly, Lien and colleagues (2016) reported higher serum oxytocin in patients with bipolar II disorder relative to patients with major depression and healthy controls. In contrast to Turan and colleagues' finding however, Lien and colleagues found that following treatment, oxytocin levels of bipolar patients, but not depressed patients, were reduced.

Higher levels of serum oxytocin have also been observed in adolescents with treatment-resistant depression – which predicts later development of bipolar disorder, major depression, and schizophrenia – when compared to healthy control subjects and subjects with treatment-responsive depression (Sasaki et al., 2016). Subclinical manic symptoms tend to predict poor response to depression treatment in both adolescents and adults (Correa et al., 2010; Maalouf et al., 2012). If mania is associated with elevated oxytocin as noted above, and if mania predicts poor response to treatment, then treatment-resistant depression is indeed expected to involve elevated levels of oxytocin.

Increased oxytocin levels are also associated with traits, symptoms, and disorders that belong to the psychotic-affective spectrum, of which bipolar disorder overlaps with in terms of symptoms and causes, including the tendency toward hyperactive social cognition (reviewed in Crespi, 2016). Findings on the link between elevated oxytocin and psychotic-affective symptoms are heterogeneous but compelling. For example, serum oxytocin positively predicted schizotypal traits in healthy females (Tseng et al., 2014) as well as delusional ideation in patients with schizophrenia (Walss-Bass et al., 2013). In patients with bipolar disorder, plasma oxytocin levels have been positively associated with the ability to accurately recognize fearful emotions, but not other kinds of emotions (Tas et al., 2015), which is consistent with oxytocin as a signal of social vulnerability. Evidence from psychiatry, personality, and genetic research thus indicates that oxytocin, in conjunction with dopamine, contributes to extraversion, openness, and creativity, which together involve behavioural activation, and when expressed in more extreme levels, underlie risk and expression of mania and bipolar spectrum disorders. Additional integrative endocrine, personality, and psychiatric studies are required, however, to evaluate these ideas further, especially in the contexts of sex differences, and mania and hypomania in relation to depression.

2.3.2. Oxytocin and Endometriosis

Both endometriosis and adenomyosis centrally involve altered and increased uterine peristalsis, a complex and cyclical process necessary for sperm transport and embryo positioning that is regulated through oxytocin's interactions with gonadal hormones (Kunz et al., 1998; Kunz & Leyendecker, 2002; Leyendecker et al., 1996; Kunz et al., 2007). Uterine peristalsis involves continuous wave-like patterns of rhythmic contractions that shift according to the phase of the menstrual cycle (Kunz & Leyendecker, 2002; Leyendecker et al., 2004). In healthy uteri, contractions move from the cervix to the fundus after menstruation until ovulation; this upward motion during the proliferative phase assists sperm transport from the vagina toward the fallopian tube ipsilateral to the dominant follicle. After ovulation (during the secretory phase), contractions move from the isthmus (above the cervix) to the fundus, encouraging implantation near the top of the uterus. If fertilization does not occur in a given menstrual cycle, contractile waves then move from the fundus toward the cervix, supporting the flow of menstrual blood out of the uterus.

Changes in the direction, frequency, and amplitude of uterine contractions depend in part on temporal and spatial changes in the density and distribution of uterine oxytocin receptors (Kunz et al., 1998). In women with endometriosis or adenomyosis, uterine peristalsis is stronger and faster (hyperperistalsis) as well as asynchronous with the menstrual cycle (dysperistalsis). Table 2.2 compares oxytocin-mediated uterine and menstrual characteristics in women with and without endometriosis. Although Table 2.2 focuses on endometriosis, women with adenomyosis also show overexpression of oxytocin receptors in the myometrium (Zhang et al., 2015), which may contribute to the intensity of uterine contractions and severity of dysmenorrhea, as suggested in studies on oxytocin activity and endometriosis (Guo et al., 2013; Mechsner et al., 2010; Nie et al., 2010). Elevated oxytocinergic activity thus significantly contributes to the primary features – uterine hyperperistalsis and dysperistalsis - of endometriosis and adenomyosis.

Table 2.2 Comparison of uterine activity and oxytocin characteristics in women with and without endometriosis

Women with Healthy Uteri	Women with Endometriosis
Temporal and spatial changes in uterine oxytocin receptor (OXTR) expression across the cycle[1, 2] Proliferative > secretory Proliferative: fundus < isthmus Secretory: fundal > isthmus	Higher OXTR expression in proliferative and secretory phases relative to healthy uteri[1] and no change across cycle Proliferative = secretory Proliferative: fundus ≥ isthmus Secretory: fundus ≥ isthmus
Smooth, wave-like uterine contractions that shift in direction and intensity across the cycle	At proliferative phase, wave frequency is doubled relative to healthy uteri and prior to ovulation, contractions are convulsive[5]
Directed sperm transport coincides with ovulation	At early proliferative phase, labeled particles move very rapidly relative to healthy uteri, but prior to ovulation, transport is absent[5]
Clinically non-significant menstrual pain	Dysmenorrhea[4] severity positively associated with uterine OXTR expression[1]
Mild retrograde menstruation occurs in nearly all women[3]	Retrograde menstruation results in endometrial tissue proliferating into lesions outside the womb[3]
Normal plasma oxytocin levels	Elevated plasma oxytocin levels[6]

References: 1) Huang et al 2017; 2) Zhang et al 2015; 3) Leyendecker et al 2004; 4) Harada 2013; 5) Leyendecker et al 1996; 6) He et al 2016

2.3.3. Overlapping Menstrual Characteristics Between Endometriosis and Bipolar Disorder

Some menstrual features appear to overlap between bipolar disorder and endometriosis, possibly reflecting shared disruptions of HPG axis. Shorter menstrual cycles (≤ 28 days) are associated with endometriosis (Arumugam & Lim, 1997; Cramer et al., 1986; Wei et al., 2016; Yasui et al., 2015); and adenomyosis (Templeman et al., 2008), though the causal direction of this relationship is unclear. Treloar and colleagues (2010) reported a similar but non-significant trend of short menstrual cycles predicting endometriosis risk, and also reported that earlier onset of menarche predicted later endometriosis. Similarly, Templeman and colleagues (2008) found that early menarche (≤ 10 years) predicted later adenomyosis but not endometriosis, while Missmer and colleagues (2004) reported that early menarche was a risk factor for endometriosis.

Women with bipolar disorder experience early onset menstrual dysfunction significantly more frequently than both non-depressed women and women with major

depression, which may be due to bipolar disorder-specific alterations in HPG axis functioning (Joffe et al., 2006). Short menstrual cycles (≤ 28 day cycles) were associated with an almost doubled risk of mood and substance abuse disorders in Caucasian women, but not in African-American women (Barron et al., 2009). Early menarche did not predict later onset of bipolar disorder, but was associated with longer depressive episodes and more severe depressive and cyclothymic symptomology (Kesebir et al., 2013). These lines of evidence suggest that menstrual features and menstrual dysfunction overlap between endometriosis and bipolar disorder, indicating that HPG axis dysfunction may underlie important aspects of both conditions.

2.3.4. Effects of Estrogenic and Other Medications on Endometriosis and Bipolar Disorder

Additional, indirect evidence for HPG axis alterations in endometriosis and bipolar disorder comes from the pharmaceutical literature, as medications that treat these conditions often target this axis. Table 2.3 lists several medications that interact with the HPG axis, including drugs that alter estrogen levels, which have shown positive effects on both bipolar disorder and endometriosis symptoms. For example, tamoxifen, a selective estrogen receptor modulator, is an effective anti-manic that paradoxically can both treat and induce endometriosis and adenomyosis symptoms (Table 2.3). These mixed effects are attributable to tamoxifen's interactions with estrogen: normal rats with induced endometriosis show lesion reduction when treated with tamoxifen, but after an ovarectomy, tamoxifen treatment causes the recurrence of endometriosis lesions (Kadaba & Simpson, 1990). The ability of tamoxifen to reduce endometriosis lesions in both humans and rats, under specific hormonal conditions, are likely due to the drug's inhibiting effects on estrogen-dependent cellular proliferation, an effect that is potentiated by oxytocin (Gimpl et al., 2001).

Endometriosis is an estrogen-dependent disease and estrogen is known to influence bipolar spectrum traits in women, often eliciting both depressive and manic episodes (Kumar et al., 2011; Meinhard et al., 2014; Teatero et al., 2014). Estrogen potentiates the effects of oxytocin, and its presence is often required for oxytocin-dependent traits to emerge (e.g. lordosis in rats; reviewed in Gordon et al., 2011). For example, the uterine hyperperistalsis typical of endometriosis is similar to that observed in healthy women with naturally high estrogen levels who have received intravenous

injections of oxytocin (Leyendecker et al., 1998). The oxytocin antagonist, atosiban, reduces endometriosis lesions in rats (Simsek et al., 2012), but in contrast, Yeniel and colleagues (2014) found that oxytocin itself reduced endometriosis lesions in rats, possibly through its anti-inflammatory effects. Whether or not oxytocin antagonists could be used to reduce manic symptoms is currently unknown. These medications highlight complex interactions between oxytocin and estrogen, and the HPG axis more generally, and while their effects are not fully understood, these medications are suggestive of etiological overlap between endometriosis and bipolar disorder.

Table 2.3. Effects of medications on bipolar disorder, endometriosis, and adenomyosis

Medication & Mechanism	Effect on Bipolar Disorder	Effect on Endometriosis	Effect on Adenomyosis
Valproate (Suppresses estrogen)	Commonly prescribed to treat bipolar disorder	Suppressed proliferation of endometrial stromal cells[1]	Eradication of dysmenorrhea and 1/3 reduction in uterus size[2]
Danazol (Androgenic properties)	Alleviated rapid-cycling affective symptoms and manic grandiosity in one female patient[3]	Long history of use in endometriosis; reduces pain and lesion volume[4]	Reduced pain, bleeding, and uterine size[7]
Tranylcypromine (Monoamine oxidase inhibitor)	Improved depressive symptoms and reduced switching into hypomania[6]	Significantly reduced lesion size and proliferation and pain in mice with induced endometriosis[5]	Unknown
Mifepristone (Anti-progesterone)	Improved spatial working memory, which tends to be reduced in bipolar[8]	Alleviated symptoms when used alone, and improved pregnancy rate when combined with other therapies[9]	Initiated cell apoptosis via increasing caspase 3 expression, which could inhibit adenomyosis[10]
Medroxy-progesterone (Progesterone like, anti-estrogenic)	Reduced acute mania in women with schizoaffective disorder and bipolar affective disorder when used with mood stabilizers[11]	Causes endometrial tissue atrophy but high recurrence rates after discontinuation of use[16]	Unknown
Tamoxifen (complex anti-estrogenic and estrogenic effects)	Produced anti-manic effects in 4 studies[12]	Improved symptoms in two women[15] but worsened symptoms in post-menopausal women[13]	Induces adenomyosis in mice[14]

References: 1) Wu & Guo 2008; 2) Liu & Guo 2008; 3) Goldstein 1986; 4) Godin & Marcoux 2015; 5) Sun et al 2016; 6) Heijnen et al 2015; 7) Pontis et al 2016; 8) Watson et al 2012; 9) Zhang 2016; 10) Wang et al 2014; 11) Kulkarni et al 2014; 12) Meinhard et al 2014; 13) Rose et al 2000; 14) Parrott et al 2001; 15) Haber & Behelak 1987; 16) Rodgers & Falcone 2008

2.3.5. Fitness Correlates and Impacts of Bipolar Disorder and Endometriosis

An evolutionary perspective on health and disease can help to explain why diseases persist even when they produce deleterious effects on individual fitness (Williams & Nesse, 1991). One hypothesis for the persistence of mental illness is that genetic variants contributing to psychiatric disorders also confer reproductively beneficial traits, such as enhanced creativity or intelligence, as evidenced by increased fecundity or elevated levels of beneficial traits in families of people with psychiatric diagnoses (e.g. Greenwood, 2017). Variation in personality traits such as extraversion may be maintained through tradeoffs in different combinations of fitness costs and benefits; for example, higher extraversion in women predicts higher numbers of lifetime sex partners, but also increases offspring exposure to stepparents, which constitutes a 'risky' parenting strategy (Nettle, 2005). Extraversion genes contribute to the bipolar spectrum (Lo et al., 2017), and non-affected twins of individuals with bipolar disorder demonstrate elevated positive temperaments and enhanced verbal intelligence (Higler et al., 2014). These 'attractive' traits appear to enhance mating opportunities (Nettle, 2005), helping to account for the persistence of bipolar spectrum traits and alleles in the general population.

Other studies report associations between enhanced fecundity and the bipolar spectrum. Power and colleagues (2013) investigated the relationship between several psychiatric diagnoses and number of offspring in a cohort of over two million people from a Swedish registry. While people with a bipolar diagnosis had fewer children relative to the general population, sisters - but not brothers - of people with bipolar disorder had more children relative to the general population. Increased fecundity in sisters of people with bipolar disorder suggests that genes contributing to the bipolar spectrum differentially affect female and male fitness. However, another dataset drawn from the National Comorbidity Study (n = 8098) revealed that bipolar symptoms positively predicted increased fertility, and reduced parenting effort, at younger ages in both sexes (Jacobson, 2016). Association of bipolar symptoms with reduced parenting effort is consistent with Nettle's (2005) finding that extraversion predicts riskier parenting strategies. Overall, bipolar spectrum features appear to enhance mating opportunity and fecundity, while severe bipolar disorder leads to reduced reproductive success.

Endometriosis is clearly associated with significant reductions in fertility, making its relatively high prevalence puzzling from an evolutionary perspective. Rates of mild endometriosis appear to be increasing in North America over the past few decades, but prevalence rates are difficult to accurately estimate due to changes in diagnostic criteria over the same time period (Koninckx et al., 2016). Modern environmental factors such as stress, chemical disruptors, and delayed pregnancy appear to contribute to rising rates of mild, but not severe, endometriosis (Koninckx et al., 2016). Because pregnancy-mediated progesterone release inhibits estrogen-dependent endometrial proliferation, pregnancy can prevent and improve endometriosis symptoms, and due to the social trend of women postponing childbirth to develop professionally, endometriosis has been dubbed the 'career woman's disease' (Koninckx et al., 2016). Even if current rates of endometriosis partially reflect environmental factors, evolutionary pressures are still expected to have shaped the physiological mechanisms that are sensitive to disruption in this condition.

Sperm transport mechanisms, which are essential to fertility, appear to be overdeveloped, and thus dysfunctional, in women with endometriosis (Kissler et al., 2007; Kunz et al., 2007; Leyendecker et al., 1996). Fertility depends upon cyclical uterine activity: in healthy women, elevated uterine peristalsis prior to ovulation promotes rapid sperm transport and reduced uterine peristalsis after ovulation supports conception and implantation (IJland et al., 1997; Leyendecker et al., 1996; Kunz & Leyendecker, 2002; Kissler et al., 2007). In endometriotic uteri, hyperperistalsis is sustained throughout the cycle, promoting extremely rapid uptake of sperm-like particles too early in the ovulatory cycle (Table 2.2; Leyendecker et al., 1996), and following ovulation, peristaltic dampening fails to occur, which appears to prevent implantation (Kunz & Leyendecker, 2002). Uterine hyperperistalsis and dysperistalsis thus interfere with the normal functioning of the sperm transport mechanism - specifically in the direction of hyperactivity - in women with endometriosis.

These features of endometriosis and the bipolar spectrum that demonstrate important associations with fertility and fecundity are regulated by oxytocin. Polymorphisms in the oxytocin receptor gene (OXTR) show associations with childbirth at younger ages, plus reduced usage of contraceptives (Prichard et al. 2007). A recent study found that women with the A allele of the widely studied OXTR SNP rs53576 reported higher rates of orgasm and sexual arousal when the allele co-occurred with a

specific estrogen receptor allele (Armeni et al., 2017). Relative to the G allele of OXTR rs53576, the A allele predicted generally reduced prosocial behaviour in a meta-analysis (Li et al., 2015). Two studies have found associations between duration of labour and rs53576 alleles, but the results were in opposite directions (Reitman et al., 2011; Terkawi et al., 2012). Variation in oxytocin genes thus jointly influence sociality, sexual behaviour, and reproductive functioning in women, and though results are mixed and effect sizes small, these findings highlight the diverse, pleiotropic, and fitness-relevant effects of the oxytocinergic system.

2.3.6. Oxytocin, Autism, and Polycystic Ovary Syndrome

If elevated oxytocinergic activity jointly contributes to bipolar disorder and endometriosis, then reduced oxytocinergic activity should jointly underlie diseases with symptoms and causes opposite to those observed in bipolar disorder and endometriosis. A pair of psychological and reproductive disorders, autism and polycystic ovary syndrome (PCOS), appears to fit this pattern. Both autism and PCOS involve elevated androgen activity, and testosterone, one of the main androgens, demonstrates opposite effects to oxytocin across diverse cognitive, behavioural, and physiological domains (Crespi, 2016). Autism is characterized by diminished social interest, communication difficulties, and restricted or repetitive interests and behaviours (Cochran et al., 2013), and generally involves reduced activity of the oxytocinergic system (Gordon et al., 2016; Parker et al., 2014). Repetitive behaviour and restricted interests in autism can be contrasted with increased novelty-seeking in bipolar disorder (Zaninotto et al., 2016), and the autism spectrum involves reduced levels of extraversion and openness (Schwartzman et al., 2016; Strunz et al., 2015), and reduced goal pursuit through social reward (Dölen, 2015), in contrast to the elevations of these three phenotypes in bipolar disorder, as described above.

Women with autism spectrum conditions are also more likely to identify as 'asexual' compared to non-autistic women (Ingudomnukul et al., 2007), and tend to exhibit lower levels of sexual interest and activity overall (Byers et al., 2013); these findings contrast with elevated sexual motivation - sometimes to an extent that is characterized as hypersexuality - in women with bipolar disorder (Kopeykina et al., 2016, Mazza et al., 2011). Sexual interest is mediated by oxytocin-dopamine interactions (Borrow & Cameron, 2012; Pfaus, 2009; Veening et al., 2015). These findings indicate

that some oxytocin-mediated psychological and behavioural features show evidence of opposite patterns in autism and bipolar disorder, though comparisons between these two disorders should be interpreted with caution due to significant differences in age of onset between the two conditions.

Women with autism spectrum conditions, as well as their female relatives, frequently display comorbid testosterone-related disorders, including PCOS (Ingudomnukul et al., 2007), and offspring of mothers with PCOS demonstrate elevated levels of autistic features and autism diagnoses (Kosidou et al., 2016; Palomba et al., 2012;). PCOS is a reproductive condition affecting 4 - 18% of women of reproductive age that involves symptoms related to hyperandrogenism including increased body hair (hirsutism), irregular or absent menstruation, ovarian dysfunction with irregular or absent ovulation, and metabolic alterations including insulin resistance and increased risk of cardiovascular disease (Teede et al., 2010). Although oxytocin levels in women with PCOS have not been assessed to the best of our knowledge, several key features of the condition are suggestive of low oxytocinergic activity, and these contrast with features of endometriosis.

First, uterine peristalsis in women with PCOS was undetectable in one study, which may indicate reduced uterine contractility in women with this condition (Leonhardt et al., 2012). Second, women with PCOS display thinner endometria (Leonhardt et al., 2012), while women with adenomyosis tend to have thicker endometria (Benagiano et al., 2014). Endometrial thinning in PCOS may be due to high levels of the testosterone precursor androstenedione, as androstenedione inhibits human endometrial cell growth (Tuckerman et al., 2000), and is elevated in people with autism and in women with PCOS (Georgopoulos et al., 2014; Ruta et al., 2011). Third, women with PCOS tend to have irregular menstrual cycles with infrequent or absent ovulation (Teede et al., 2010), while women with endometriosis tend toward shorter cycles with intact ovulation (Hughes et al., 2007). Fourth, while valproate reduces the size of endometriosis lesions and treats symptoms of bipolar disorder (Table 2.3), it can induce polycystic ovaries when taken by women for epilepsy (Isojärvi et al., 1993); prenatal valproate also represents a well-validated cause of high autism risk in offspring (Roullet et al., 2013).

Polycystic ovary syndrome contrasts notably with endometriosis for the hormone-related physical characteristics waist-to-hip ratio and body mass index, such that these

two indices are increased in the former condition but decreased in the latter, compared to controls (Backonja et al., 2016; Ezeh et al., 2014; Shah et al., 2013; Velázquez et al., 2000); these findings are also of interest given evidence of higher fertility being associated with lower waist to hip ratios, in a typical population (Jasienska et al., 2004). Lower levels of serum testosterone (and high estradiol) have also been reported in endometriosis patients (Ono et al., 2014), in comparison to the high testosterone characteristic of women with PCOS. Serum oxytocin is lower in women with obesity or newly-diagnosed type 2 diabetes, compared to controls (Qian et al., 2014), which is consistent with its demonstrated effects on metabolism, energy balance, and body weight (Blevins & Ho, 2013); however, as noted above, the oxytocin system remains virtually unstudied in patients with PCOS.

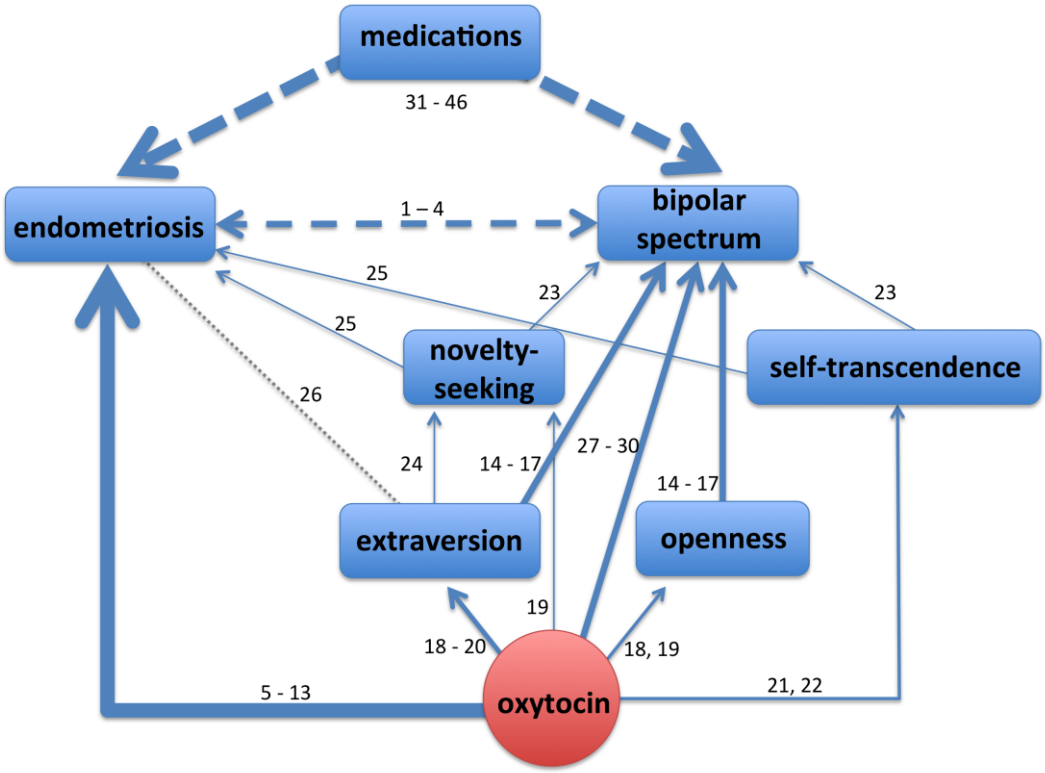
Considered together, these findings demonstrate that physical, physiological and behavioural features of co-occurring autism and PCOS contrast with features of bipolar disorder and endometriosis, and further, that these diametric patterns of features may be associated with relatively reduced versus elevated oxytocinergic activity. At this time there is no evidence for PCOS as a condition of low oxytocin, although many women with PCOS experience obesity and increased risk for type 2 diabetes, two features associatd with low oxytocin levels. Future joint studies of endometriosis, and PCOS, in relation to controls, are clearly warranted.

2.4. Discussion

We have described diverse lines of evidence from personality research, endocrinology, psychiatry, and medicine that converge to support the hypothesis that elevated oxytocinergic activity contributes to the symptoms and features of, and the comorbidity between, bipolar disorder and endometriosis (Figure 2.3). Evidence for shared etiology of these conditions is especially valuable when considered in two contexts. First, endometriosis and bipolar disorder provide a paradigmatic example of how comorbid diseases can arise through altered activity of a pleiotropic system. Further, the symptoms of these conditions reveal evidence for apparently-adaptive pleiotropy in the female oxytocin system, as bipolar and endometriosis features appear to reflect extreme - and disrupted - manifestations of phenotypes that normally enhance reproduction when co-occurring within individuals. Second, the oxytocin system emerges

as a key research avenue for elucidating the causes of women's increased susceptibility to conditions that centrally involve joint mind-body disturbances.

Figure 2.3 Evidence-based, oxytocin-mediated interrelationships between personality traits, endometriosis, and the bipolar spectrum



The weight of the arrows between variables estimates the relative strength of evidence for positive associations between the variables, based on the number of studies reviewed. Because the arrow widths are based only on the studies included in our review, some of the arrow weights are underestimated (e.g. novelty-seeking with extraversion and bipolar), as the extensive literature documenting their overlap was not central to our review. Dashed lines represent mixed evidence, and the single dotted line (between endometriosis and extraversion) signifies negative evidence, as Low and colleagues (1993) reported that women with endometriosis displayed reduced extraversion relative to unaffected women.

References: 1) Kumar et al 2011; 2) Lewis et al 1987; 3) Walker et al 1989; 4) Osório et al 2016; 5) Huang et al 2017; 6) Zhang et al 2015; 7) Leyendecker et al 2004; 8) Harada 2013; 9) Leyendecker et al 1996; 10) He et al 2016; 11) Guo et al 2013; 12) Nie et al 2010; 13) Mechsner et al 2010; 14) Quilty et al 2009; 15) Durbin et al 2008; 16) Meyer 2002; 17) Lo et al 2017; 18) Cardoso et al 2012; 19) De Dreu et al 2015; 20) Andari et al 2012; 21) Van Cappellen et al 2016; 22) Crespi & Summers 2014; 23) Zaninotto et al 2016; 24) Zuckerman & Glicksohn 2016; 25) Facchin et al 2016; 26) Low et al 1993; 27) Turan et al 2013; 28) Saskai et al 2016; 29) Tas et al 2015; 30) Lien et al 2016; 31) Wu & Guo 2008; 32) Liu & Guo 2008; 33) Goldstein 1986; 34) Godin & Marcouz 2015; 35) Sun et al 2016; 36) Heijnen et al 2015; 37) Pontis et al 2016; 38) Watson et al 2012; 39) Zhang 2016; 40) Wang et al 2014; 41) Kulkarni et al 2014; 42) Meinhard et al 2014; 43) Rose et al 2000; 44) Parrott et al 2001; 45) Haber & Behelak 1987; 46) Rodgers & Falcone 2008

The evidence for comorbidity between endometriosis and bipolar disorder is intriguing but not unambiguous (Table 2.1), as two studies found support for their linkage (Kumar et al., 2011; Lewis et al., 1987) and two did not (Osório et al., 2016; Walker et al., 1989). Chronic pelvic pain is generally predictive of mood disorders (Osório et al., 2016), so the specificity of the linkage between endometriosis and the bipolar spectrum requires further testing. All four studies that assessed bipolar disorder prevalence in women with endometriosis invoked clinical instruments and diagnostic thresholds, meaning that women presenting with mild bipolar symptoms may miss diagnostic thresholds, which could underestimate overlap between endometriosis and the bipolar spectrum. Diagnostic categories do not reflect underlying etiological factors, but rather involve heterogeneous collections of symptoms that tend to cluster together while engendering significant levels of personal impairment (Wardenaar & de Jonge, 2013). The hypothesis addressed here does not require that women with endometriosis meet criteria for a clinically significant bipolar disorder, but rather predicts that women with endometriosis manifest personality traits and psychological features that are caused, in part, by increased oxytocinergic activity. Examining women with endometriosis using dimensional assessments of oxytocin-mediated bipolar spectrum traits would provide a stronger test of the hypothesis, compared to categorical instruments that apply strict thresholds. Such an approach did support the hypothesis, as women with endometriosis demonstrated higher levels of psychoticism, impulsiveness, and aspects of self-transcendence (Facchin et al., 2016; Low et al., 1993), but also reduced extraversion (Low et al., 1993), which contrasts with predictions. These preliminary trends thus need to be further clarified in larger samples of women, with appropriate controls for pain, using a broader range of questionnaires that quantify oxytocin-mediated, bipolar spectrum personality features, such as mania and hypomania, the tendency to exhibit spiritual experiences, novelty-seeking, creativity, extraversion, and openness (Table 2.4).

Emerging evidence reveals oxytocin's role in motivating complex social cognition (Crespi, 2016). Under our hypothesis, women with endometriosis are predicted to display heightened mentalistic and emotion-recognition skills, and perhaps elevated rumination concerning social interactions (Table 2.4). These elevations may only occur for specific domains of social cognition, such as enhanced recognition of negative but not positive emotions (e.g. Tas et al., 2015), or they might involve increased attention to

social threats or relationships, as elevated oxytocin levels can be indicative of prolonged social stress and relationship vulnerability (Crespi, 2016; Grebe et al., 2017). To the best of our knowledge, mentalizing has not been studied in women with endometriosis, and careful controls for pain levels must be included as pain could diminish concentration and performance in a variety of tasks. Another approach to testing the hypothesis involves studying cognitive phenotypes, such as visual-spatial skills, in women with endometriosis, as social and non-social cognition display diametric associations with oxytocin and appear to trade off with one another (Crespi, 2016). Visual-spatial abilities are negatively related to serum oxytocin in post-menopausal women (Kocoska-Maras et al., 2013), reduced in people with bipolar disorder (Watson et al., 2012), and disrupted in rats following oxytocin administration (Wu & Yu, 2004), so under the hypothesis addressed here, women with endometriosis are predicted to show diminished visual-spatial abilities (Table 2.4).

Evidence for the role of increased oxytocin receptor densities in endometriosis uteri, and their role in altering uterine contractility and contributing to the symptoms of endometriosis is strong and consistent (Table 2.2). Whether or not increased oxytocin receptor densities in the uterus consistently correspond to elevated serum oxytocin remain unknown, but given the dependence of both uterine and serum oxytocin on oxytocin system genes (OXT and OXTR), it is expected that there is some general tendency toward higher oxytocin levels and higher uterine oxytocin receptor densities in women with endometriosis, and in women with bipolar disorder. Under the hypothesis addressed here, it is expected that women with bipolar disorder have elevated levels of uterine peristalsis relative to women without bipolar disorder, as measured using ultrasound or other approaches (Table 2.4). Such a study would help elucidate the relationships between serum oxytocin, uterine oxytocin, and uterine activity.

Evolutionarily framing the connection between endometriosis and the bipolar spectrum means understanding the features of each condition, as well as their comorbidity, as extensions or alterations of normally adaptive psychological and reproductive processes. Both endometriosis and bipolar disorder are intimately tied to the female reproductive cycle, in that the onset and symptoms of each condition are influenced by hormonal fluctuations and reproductive phase (Bloski & Pierson, 2008; Teatero et al., 2014). The pronounced, hormonally regulated, cyclical growth and shedding of the endometrium in human females was likely an evolutionary response to

the deep and invasive placentation characteristic of our species, which supported the evolution of our species' large and socially intelligent brains (Strassman, 1996; Cole, 2015). Both endometriosis and bipolar disorder involve alterations to the cyclical nature of female reproduction. Endometriosis is associated with shorter menstrual cycles (Arumugam & Lim, 1997; Cramer et al., 1986; Wei et al., 2016; Yasui et al., 2015). Women with bipolar disorder experience rapid cycling between depressive and manic states more frequently and more severely than men with bipolar disorder (Erol et al., 2015). That both endometriosis and bipolar disorder involve altered, rapid cycling, with associated affective and reproductive features, suggests that the relatively recent evolution of especially-invasive placentation in the human lineage, and the sensitive mechanisms that interact with it, especially high endometrial proliferation and copious menstruation, has generated new vulnerabilities to disease-related disruption.

Considering the large body of evidence for oxytocin's diverse positive effects on sociality and reproduction, selection on the oxytocin system may involve a 'cliff-edged' fitness function (Nesse, 2004) where increasing levels of oxytocin are associated with increasing fitness benefits until a certain threshold, where fitness drastically drops. For example, stronger cervico-fundal contractions are associated with increased pregnancy rates in women undergoing intrauterine insemination (Kim et al., 2015), which may or may not be true for natural pregnancies (see IJland et al., 1997); if increased uterine contractility, up to a certain threshold, enhances sperm transport and conception, selection may have driven oxytocin-mediated uterine contractility to this 'cliff-edge'. Assessing the fecundity of unaffected female relatives of women with endometriosis would help explore this hypothesis (Table 2.4), because if sperm transport in women with endometriosis has surpassed the cliff edge, then it might be expected that unaffected relatives share oxytocinergic genetic variation that improves sperm transport and thus fertility.

Table 2.4. Predictions and suggested data collection to test the proposed hypothesis

Prediction	Data Required
Women with endometriosis show higher levels of bipolar spectrum traits such as hypomania, impulsivity, openness, extraversion, self-transcendence and creativity.	Compare personality traits between women with and without endometriosis, including controls for pain levels, such as a pain-free endometriosis group, or a control group with pelvic pain but no endometriosis.
Women with endometriosis show conserved or elevated mentalizing skills relative to women without endometriosis.	Compare 'Reading the Mind in the Eyes' performance between groups, or emotion recognition tasks, with controls for pain.
Women with endometriosis show cognitive phenotypes that are associated with high oxytocin levels and bipolar disorder, including reduced visual-spatial skills.	Compare mental rotation test scores between women with and without endometriosis. Include measures of pain as a possible confounding variable.
First-degree, unaffected relatives of women with endometriosis show higher levels of bipolar spectrum traits such as hypomania, impulsivity, openness, self-transcendence, extraversion, and creativity.	Assess personality traits of first-degree relatives of women diagnosed with endometriosis.
First-degree female relatives of people with bipolar disorders have elevated rates of endometriosis compared to families without a history of bipolar disorders.	Large epidemiological study assessing rates of endometriosis relative to bipolar disorder.
Women with bipolar disorder have elevated uterine contractility relative to women without bipolar disorder.	Assess uterine contractility in women with bipolar disorder compared to healthy controls using transvaginal sonography.
Unaffected female relatives of women with endometriosis have increased fecundity.	Large population study of birth rates in relatives of women with endometriosis.
Subclinical endometriosis is associated with increased fertility.	Difficult to assess as the boundary between subclinical and clinical endometriosis can depend on pain, and women not experiencing pain may not visit clinics or be aware of possible endometriosis.
Oxytocin antagonists improve bipolar symptoms, specifically mania.	If deemed safe and ethical, give oxytocin antagonists to people with bipolar disorder and measure effect on manic symptoms.

Oxytocin, through its interactions with gonadal hormones, enhances sexual interest and promotes sperm transport during the fertile window of the ovulatory cycle (Borrow & Cameron, 2012; Salonia et al., 2005). These features suggest adaptive coordination in the female oxytocinergic system, such that women who are relatively highly motivated to engage in sexual and social relationships may also demonstrate enhanced fertility. Together, endometriosis and bipolar disorder may thus reflect an

extreme, dysfunctional manifestation of a highly social/highly fertile, 'fast' life history strategy. Characterizing bipolar disorder as a fast life history strategy is consistent with Del Giudice's (2014) placement of psychological disorders along a life history axis, and may contrast with a less social, low fertility, and 'slow' life history strategy represented by the autism spectrum (Del Giudice, 2014) and co-occurring PCOS.

The primary limitations of the hypothesis presented and evaluated here are that many of the predictions have yet to be subject to targeted tests, that much of the evidence is correlative and indirect, and that both endometriosis and bipolar disorder are mediated by a range of causal factors, many of which are certainly independent of the oxytocinergic system. Notwithstanding, a notable diversity of convergent evidence supports the hypothesis, and the predictions that it makes, with regard to these disorders, as well as autism and PCOS, are clear, specific, and testable, with important implications in both clinical and non-clinical domains.

Although we know that the womb in its entirety does not migrate throughout the body to cause female distress, it is interesting, given the contributions of oxytocin to both endometrial activity and psychological traits, that early observers and medical practitioners assumed a connection between uterine activity and mental health. Indeed, somatic symptoms are highly prevalent in female-preponderant mental disorders, especially in disorders linked to trauma, such as dissociative disorder, post-traumatic stress disorder, borderline personality disorder, and also depression and anxiety (Seng, 2010). Comorbid physical health issues such as irritable bowel syndrome, gastrointestinal issues, genitourinary issues, pelvic pain, and increased nausea and vomiting during pregnancy are commonly observed in these female-biased psychiatric diagnoses (Seng, 2010; Seng et al., 2013). Seng (2010) and colleagues (2013) proposed that trauma dysregulates the oxytocinergic system and due to oxytocin's multiple effects in the brain and body, heterogeneous physical, emotional, and interpersonal symptoms tend co-occur in people who have experienced trauma. This hypothesis overlaps with the one addressed here, in terms of oxytocin's ability to jointly regulate reproductive and psychological traits that when disturbed, become symptoms of multiple disorders. The oxytocin signal is crucial to female reproductive success because of its joint roles in parturition, lactation, and maternal care; these female-specific functions may help explain, in part, why women are especially vulnerable to symptoms and conditions that centrally involve joint mind-body disturbances.

Interpretations of medical causes that focus upon sex-specific biology should be critically approached, because the environment - including societal and cultural factors - also influences the onset, course, symptoms, and diagnosis of disease (Kirmayer & Pedersen, 2014). For example, in Hippocrates' era, it was accepted that only women could suffer from hysteria (Figure 2.1), and this belief promoted female-specific explanations and treatments for hysteria, while simultaneously justifying the reduced participation of women in society (Allison & Roberts, 1994; Devereux, 2014). Much later, during the Industrial Revolution, psychoanalysts observed hysteria in males as well, which motivated alternative explanations for hysteria's etiology (Novais et al., 2015). More recently, it has been observed that people in countries undergoing westernization, a process that involves sudden and massive changes to traditional ways of life, express higher rates of hysteria-like symptoms than people in westernized societies (reviewed in Tasca et al., 2012). Furthermore, the somatic and dissociative symptoms formerly labeled as hysteria show significant and compelling overlap with the human response to trauma (vanderKolk et al., 1996; vanderKolk et al., 2005). These fluctuating and environmentally dependent incidences of hysteria-related symptoms have been used to support the idea that one can use the prevalence of hysteria-like conditions in a given region as an index of the current level of social restrictiveness experienced by a population (Devereux, 2014). These findings, considered together with evidence for early-life organizational effects on the oxytocinergic system (Johnson & Buisman-Pijlman, 2016), indicate that future studies of bipolar disorder and endometriosis should take into account societal and cultural factors, in addition to individual factors, especially those involving exposure to trauma.

The hypothesis evaluated here intersects with multiple challenges in the study of health and disease, including the limitations of diagnostic categories, the problematic nature of studying 'mind' as separate from 'body', and the complex role of evolved sex differences in shaping differential susceptibility to disease. If supported by further evidence, the hypothesis has immediate practical applications, as women diagnosed with endometriosis might be assessed for comorbid bipolar disorder, and if women with bipolar disorders experience pelvic pain, the possibility of endometriosis could be investigated. Also, treatments and therapies that address women's health from an integrated mind-body perspective may be beneficial to women with these conditions (Meissner et al., 2010; Rusner et al., 2010). Although the hypothesis oversimplifies the

complexity of the oxytocinergic system, it should help to guide future research toward novel and productive avenues, to further explore how positively pleiotropic systems underlie correlated patterns of disease. The 'wandering womb' of the past may indeed contain some truth, as enhanced wellbeing of women emerges through the joint optimization of reproductive, physiological, and psychological health.

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Chapter 3.

Endometriosis and Polycystic Ovary Syndrome are Diametric Disorders

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3.1. Abstract

Evolutionary and comparative approaches can yield novel insights into human adaptation and disease. Endometriosis and polycystic ovary syndrome each affect up to 10% of women and significantly reduce the health, fertility, and quality of life of those affected. Polycystic ovary syndrome and endometriosis have yet to be considered as related to one another, although both conditions involve alterations to prenatal testosterone levels and atypical functioning of the hypothalamic-pituitary-gonadal axis. Here we propose and evaluate the novel hypothesis that endometriosis and polycystic ovary syndrome represent extreme and diametric (opposite) outcomes of variation in hypothalamic-pituitary-gonadal axis development and activity, with endometriosis mediated in notable part by low prenatal and postnatal testosterone, while polycystic ovary syndrome is mediated by high prenatal testosterone. This diametric disorders hypothesis predicts that, for characteristics shaped by the hypothalamic-pituitary-gonadal axis, including hormonal profiles, reproductive physiology, life history traits, and body morphology, women with polycystic ovary syndrome and women with endometriosis will manifest opposite phenotypes. To evaluate these predictions, we review and synthesize existing evidence from developmental biology, endocrinology, physiology, life history, and epidemiology. The hypothesis of diametric phenotypes between endometriosis and polycystic ovary syndrome is strongly supported across these diverse fields of research. Furthermore, the contrasts between endometriosis and polycystic ovary syndrome in humans parallel differences among non-human animals in effects of low versus high prenatal testosterone on female reproductive traits. These findings suggest that polycystic ovary syndrome and endometriosis represent maladaptive extremes of both female life history variation and expression of sexually

dimorphic female reproductive traits. The diametric disorders hypothesis for endometriosis and polycystic ovary syndrome provides novel, unifying, proximate and evolutionary explanations for endometriosis risk, synthesizes diverse lines of research concerning the two most common female reproductive disorders, and generates future avenues of research for improving the quality of life and health of women.

3.2. Introduction

Evolutionary processes shape human vulnerabilities to disease (Nesse & Stearns, 2008). Some pairs of diseases, such as autoimmunity and infection, cancer and neurodegeneration, and autism and psychosis, represent opposites to one another (Crespi & Go, 2015). Such diseases manifest in pairs because they involve dysfunction of the same general biological system, but in diametric directions. For example, higher risk of infection involves immune system under-activity whereas higher risk of autoimmune disorder involves immune system over-activity (Crespi & Go, 2015). This framework of diametric diseases provides key insights into evolutionary and medical questions, as disease pairs and their symptoms can represent extreme, maladaptive expressions of adaptations and tradeoffs.

Endometriosis and polycystic ovary syndrome (PCOS) both involve altered functioning of the female hypothalamic-pituitary-gonadal (HPG) axis, but they have yet to be considered as associated with or related to one another. Here we propose and evaluate the novel hypothesis that these two conditions represent a pair of diametric diseases. First, we describe what is known and unknown concerning the etiologies of endometriosis and PCOS. Second, we review how prenatal testosterone impacts HPG development and activity in females, specifying how different levels of prenatal testosterone should affect the HPG. Third, we describe in detail the diametric disorders hypothesis for endometriosis and PCOS risk. Fourth, we deduce six predictions from this hypothesis, reviewing each prediction through drawing on existing literature from multiple fields of study. Finally, we synthesize these diverse lines of evidence, evaluating the strength of support for the hypothesis, in addition to its implications and limitations.

The etiology of endometriosis, a condition diagnosed when endometrial tissue proliferates beyond the uterine boundaries, is highly enigmatic (Bulun et al., 2019; Burney & Giudice, 2012; Giudice & Kao, 2004). Women with endometriosis can

experience severe pelvic pain, especially during menstruation (dysmenorrhea), and heavy menstrual bleeding, as well as reduced fertility (Bulun et al., 2019).

Research into the causes of endometriosis largely focuses on explanations for how endometrial cells appear in the peritoneal cavity and other bodily sites (e.g. Sampson, 1927; Brosens et al., 2015; Sasson & Taylor, 2008), identification of predisposing genes and environmental risk factors (e.g. García-Peñarrubia et al., 2020; Rahmioglu et al., 2014), and studies of steroid and immunological pathways that promote lesion establishment and growth (e.g. García-Gómez et al., 2020; Marquardt et al., 2019). These approaches help to explain aspects of the disorder, but a unifying explanation for why some women are particularly vulnerable to endometriosis remains elusive.

Relatively more is known concerning the etiology of PCOS than endometriosis. PCOS is diagnosed when women manifest signs of hyperandrogenism (high testosterone), irregular or absent ovulation, and polycystic (multi-small follicle) ovaries; other traits, especially insulin resistance and obesity, frequently co-occur (Rotterdam, 2004). These diverse symptoms of PCOS emerge following puberty, primarily in response to elevated androgenic activity of ovarian origin (Rosenfield & Ehrmann, 2016). In response to insulin, ovaries of women with PCOS produce especially high levels of androgens while peripheral tissues demonstrate insulin resistance. Resulting hyperinsulinemia further augments androgen production, contributing to obesity in women, which further increases androgen levels via adipose tissue (Diamanti-Kandarakis & Dunaif, 2012). The metabolic and endocrine alterations observed in PCOS interact in complex ways and are rooted in early development: fetal exposure to high levels of testosterone during an early, critical window of embryological development biases the HPG axis toward increased testosterone production that continues throughout postnatal life (Abbott, Dumesic, & Franks, 2002; Abbott, Dumesic, & Levine, 2019; Filippou & Homburg, 2017; Walters et al., 2018).

The HPG axis regulates many aspects of reproduction in both sexes, including sex differentiation *in utero*, hormone production, and the pacing of reproductive events – including menarche and menopause in women - throughout postnatal life (Plant, 2015). Genitourinary structures, endocrine systems, and features of the nervous system

develop in response to sexually dimorphic levels of testosterone, with male fetuses subject to substantially higher levels of testosterone than female fetuses.

In species bearing litters, females gestating beside males are commonly exposed to elevated levels of testosterone originating from the testes of their male littermates (Vandenbergh & Huggett, 1995). In species such as humans, which typically bear singleton offspring, variation in prenatal testosterone exposure of developing females comes from the fetus itself, the placenta, and the mother's circulation, such that testosterone accumulates from numerous sources including her adrenal glands, fat tissues, and ovaries (Hakim, Padmanabhan, & Vyas, 2017). Testosterone levels thus vary between individual females, in humans and other mammals, and have important, lifelong consequences on adult morphology, physiology, behaviour, and reproduction via the development of the HPG axis (Bütikofer et al., 2019; Robinson, 2006; Ryan & Vandenbergh, 2002; Slutske et al., 2011; Tyndall et al., 2012).

Multiple causes contribute to female fetal exposure to testosterone. Maternally produced testosterone enters the placenta, but in typically developing females, most is converted into estrogens via aromatase (Kallak, Hellgren, Skalkidou et al., 2017). The metabolic alterations of PCOS contribute to placental dysfunction in affected mothers, such that increased insulin secretion reduces placental aromatase activity, exposing female fetuses to elevated testosterone (Dumesic, Hoyos, Chazenbalk et al., 2020). Fetal ovaries also respond to maternal hyperinsulinemia, evident in women with diabetes or PCOS, by upregulating androgen production, representing a maternal-fetal interaction that increases overall testosterone exposure (Dumesic et al., 2020).

Other maternal factors such as elevated stress, quantified by amniotic cortisol levels, increased maternal weight gain, and young maternal age together predict 64.3% of the variation in amniotic testosterone drawn from female fetuses (Kallak et al., 2017). Further, evidence from twin studies of serum testosterone or hormonally-mediated digit ratio measurements demonstrate that adult testosterone as well as its bioavailability demonstrate significant additive genetic effects, indicating that women who produce more testosterone will have offspring who also produce higher testosterone (Coviello, Zhuang, Lunetta et al., 2011; Stone, Folkerd, & Doody, 2009; Hiraishi, Saski, Shikishima, et al., 2012; Paul, Kato, Cherkas, et al., 2006).

When developing female embryos are exposed to relatively high levels of testosterone – such as in females who develop PCOS - many aspects of HPG activity are affected. Hypothalamic sensitivity to steroid-induced negative feedback is reduced, resulting in an increased frequency and amplitude of gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) pulses with corresponding increases in LH levels (Pastor et al., 1998; Roland & Moenter, 2014). Increased LH relative to follicle-stimulating hormone (FSH) results in elevated ovarian testosterone with subsequent arrest of follicular maturation (Burt Solorzano et al., 2012). Immature follicles release high levels of anti-Müllerian hormone (AMH), which further stimulate GnRH release while inhibiting FSH release (Franks & Hardy, 2020). The ovulation-inducing LH surge is also impaired, resulting in lengthened or absent menstrual cycles (Foecking et al., 2005; Robinson, 2006). Prenatal androgen treatment induces HPG changes as well as metabolic alterations including insulin resistance, obesity and enlarged adipocytes in female rhesus monkeys and mice (Abbott, Tarantal, & Dumesic, 2009; Roland, Nunemaker, Keller et al., 2010). Importantly, these testosterone-induced alterations to female development are largely consistent across animal models (Astapova, Minor, & Hammes, 2019; Roland & Moenter, 2014).

Contributions of high prenatal testosterone to disease risks in women are thus well understood. If and how relatively *low* prenatal testosterone contributes to disease risk in women has yet to be explored in any detail, but several clues suggest that endometriosis may represent such an outcome. First, recent findings of short anogenital distances in women with endometriosis compared with controls (Mendiola et al., 2016; Crestani et al., 2020; Peters et al., 2020) implicate low prenatal testosterone in this disorder, although these results have yet to be considered or synthesized in the context of how and why endometriosis develops. Second, women with endometriosis demonstrate atypical HPG functioning (Cahill et al., 1995; Cahill & Hull, 2000; Stilley, Birt, & Sharpe-Timms, 2012), which can reflect prenatal programming via hormonal exposure. Third, prenatal exposure to estrogenic and antiandrogenic chemicals are known to predict endometriosis risk (e.g. Missmer et al., 2004).

In contrast to the known HPG alterations induced by relatively high prenatal testosterone characteristic of PCOS, a disorder caused by relatively low prenatal testosterone should centrally involve the following alterations: (1) a lower frequency of gonadotropin-releasing hormone (GnRH) pulses reflected by reduced luteinizing

hormone (LH); (2) elevated follicle-stimulating hormone (FSH) relative to LH; (3) low ovarian and serum testosterone, and low anti-Müllerian hormone (AMH); (4) faster follicular maturation; and (5) shorter menstrual cycles. As described in detail below, all of these conditions are met by endometriosis.

The diametric model proposed here hypothesizes that risk of endometriosis is mediated in notable part by low prenatal testosterone exposure, which primes the developing HPG axis to under-produce testosterone relative to estradiol throughout adult life, contributing to the core symptoms and correlates of endometriosis. Under the diametric disorders hypothesis, endometriosis and PCOS thus represent opposite and extreme manifestations of testosterone-mediated HPG axis development and activity in women, with high levels increasing PCOS risk and with low levels increasing endometriosis risk. If this hypothesis is correct, then the risk factors, proximate causes, symptoms, and correlates of endometriosis and PCOS should be tend to be opposite to one another. We tested this hypothesis through interdisciplinary and integrative comparisons of the two disorders, using data from the literature.

3.3. Methods

We searched the endometriosis and PCOS literatures extensively for data on aspects of early development, endocrine-level physiology, physical morphology, reproductive-system physiology, life history, and epidemiology that could be compared between the two disorders. We focused especially on sets of integrated traits associated with prenatal development (including roles for testosterone), and HPA axis functioning. The findings were outlined and organized into a set of six main predictions that stem from the diametric disorders hypothesis.

3.4. Results

3.4.1. Endometriosis and PCOS are associated with low and high prenatal testosterone respectively

Sexually dimorphic morphological traits that develop under hormonal influences during specific windows of early embryological life are used as proxies for *in utero* testosterone exposure. Anogenital distance (AGD) is a sensitive and reliable biomarker

of fetal testosterone exposure across mammalian species, with elevated testosterone resulting in longer AGDs (as found in males) and reduced testosterone resulting in shorter AGDs (as found in females) (Thankamony et al., 2016). Exogenous testosterone given during early to mid-gestation increases female AGD in diverse animal models including rodents, monkeys, and sheep (Rhees et al., 1997; Hotchkiss et al., 2007; Abbott et al., 2012; DeHaan et al., 1987). High doses of prenatal estrogenic chemicals decrease AGD in rodents, apparently through their ability to suppress testosterone production (Stewart, Mattiske, & Andrew, 2018). Thus, although AGD is generally used as a proxy for prenatal testosterone exposure, AGD – and reproductive development more broadly - involves complex interactions between testosterone and estrogen (Barrett et al., 2014; Williams et al., 2001).

Studies on rodents and rabbits demonstrate linear increases in female AGD as a function of *in utero* proximity to male siblings, with the shortest AGDs measured in females with no adjacent male siblings (0M females) and the longest AGDs in females with two adjacent male siblings (2M females) (Clemens, 1974; vom Saal, 1976; vom Saal et al., 1990; Vandenbergh & Huggett, 1995; Bánszegi et al., 2009). Testosterone concentrations in blood and amniotic fluid are higher in 2M than 0M female mouse fetuses, supporting the use of intrauterine position and AGD as metrics of prenatal testosterone exposure (vom Saal & Bronson, 1980a).

Women with PCOS have significantly longer AGDs than unaffected controls (Table 3.1), supporting the hypothesis that PCOS involves elevated prenatal exposure to testosterone (Filippou & Homburg, 2017). Daughters of mothers with PCOS also demonstrate evidence of longer AGDs than daughters of unaffected women (Barrett et al., 2018; Perlman et al., 2020, but see Glintborg et al., 2019), in association with high serum testosterone in affected mothers during gestation. Clinical characteristics of PCOS, including elevated serum testosterone and increased ovarian follicle count, are also positively associated with AGD in non-clinical samples of female college students (Mira-Escolano et al., 2014; Mendiola et al., 2012).

In contrast to women with PCOS, women with endometriosis demonstrate significantly shorter AGDs than unaffected women, across three datasets (Table 3.1). The strengths of these associations of AGD with endometriosis are substantial: in Mendiola et al. (2016), 91% of females with deep-infiltrating endometriosis had AGDs

below the median value, compared with 38% of controls (OR = 41.6, p = 0.002); in Crestani et al., (2020) the mean AGD of women with any degree of endometriosis as determined by laparoscopy was significantly shorter than the AGD of control subjects (OR = 6.0, p < 0.0001); and in Peters et al. (2020), women with deep-infiltrating endometriosis had significantly shorter AGDs compared with controls (OR = 2.8, p < 0.001). Short AGD also predicts endometriosis with high specificity (91.4% in Mendiola et al., 2016; 98.6% in Crestani et al., 2020). These results strongly support the prediction that endometriosis is associated with reduced prenatal testosterone.

A second proxy for prenatal hormone exposure is the ratio of length of the second to fourth finger (2D4D) (Manning, 2011). Digit ratio reflects the ratio between testosterone and estrogen during early embryological development, with higher testosterone relative to estrogen negatively predicting 2D4D (Lutchmaya et al., 2004; Zheng & Cohn, 2011). Thus, females typically demonstrate higher 2D4D than males, and higher 2D4D predicts shorter AGD in females of humans and Rhesus macaques (Manning, 2011, Barrett, Parlett, & Swan, 2015; Abbott et al., 2012). Overall, women with PCOS exhibit lower 2D4D than controls, though not all studies report significant group differences (Table 3.1). The only study assessing digit ratio in women with endometriosis found that affected women had higher right hand 2D4D than controls, but this difference was not significant, which may be due to lack of statistical power (n = 43 in each group; Peters et al., 2020). Another study found that higher 2D4D predicts heavy menstrual bleeding and dysmenorrhea (Tabachnik et al., 2020), which are core symptoms of endometriosis.

Table 3.1 Comparison of developmental and morphological traits between women with endometriosis and women with PCOS

Trait	Trait-Hormone Relationship	Women with Endometriosis	Women with PCOS
Anogenital distance (AGD)	Reliable biomarker positively associated with early prenatal testosterone exposure (Thankamony et al., 2016)	Shorter AGD in women with endometriosis relative to unaffected women (Mendiola et al., 2016; Sánchez-Ferrer et al., 2017b; Crestani et al., 2020; Peters et al., 2020)	Longer AGD in women with PCOS relative to unaffected women (Sánchez-Ferrer et al., 2017a; Wu et al., 2017; Hernández-Peñalver et al., 2018; Simsir et al., 2019; Peters et al., 2020)
Digit ratio (2D4D)	Biomarker negatively associated with prenatal testosterone exposure (Manning, 2011)	No significant difference between women with & without endometriosis (Peters et al., 2020) Higher 2D4D in women with heavy menstrual bleeding & dysmenorrhea (Tabachnik et al., 2020)	Lower 2D4D in women with PCOS relative to unaffected women in 3/5 studies, no difference in 2/5 studies (Roy et al., 2018; Cattrall et al., 2005; Pandit et al., 2016; Lujan et al., 2010; Peters et al., 2020)
Waist-to-hip ratio (WHR)	Low WHR predicts high mid-cycle estradiol (Jasieńska et al., 2004), which increases conception probability (Venners et al., 2006) & cycle regularity (Singh & Singh, 2011) High WHR predicts high testosterone, & lower conception rates during IVF (Mondragón-Ceballos et al., 2015; Sowers et al., 2001; Van Anders et al., 2005; Zaadstra et al., 1993)	Lower WHR in women with endometriosis relative to controls (Backonja et al.,2016; Byun et al., 2020)	Higher WHR in women with PCOS relative to controls (Adali et al., 2008; Cosar et al., 2008)
Body mass index (BMI)	BMI increases with testosterone levels (Mondragón-Ceballos et al., 2015) & predicts reproductive outcomes, with reduced fecundity at BMI extremes (Gaskins et al., 2015)	Reduced BMI in affected women relative to controls (Backonja et al., 2017; Jenabi et al., 2019; Liu & Zhang, 2017), especially in severe disease, though relationship between BMI & severity is not linear (Lafay Pillet et al., 2012; Yi et al., 2009)	Above-normal BMI and obesity in PCOS women relative to controls, independent of age, geographic region, & diagnostic criteria (Balen et al., 1995; Sam, 2007; Wang et al., 2018; Lim et al., 2012)
Fat distribution	Estrogen promotes fat deposition below waist, androgens increase abdominal fat (Motta-Mena & Puts, 2016; Dumesic et al., 2016)	Fat distribution below the waist associated with endometriosis (Backonja et al., 2016)	Abdominal fat associated with PCOS, including lean women with PCOS (Carmina et al., 2007; Kirchengast & Huber, 2001; Lim et al., 2012)
Muscle mass	Androgens promote growth & maintenance of lean muscle mass (Notelovitz, 2002)	Lower muscle mass in women with endometriosis (Backonja et al., 2017)	Higher muscle mass in women with PCOS (Carmina et al., 2009)

3.4.2. Endometriosis and PCOS are associated with opposite hormonal profiles for hormones produced by, or interacting with, the HPG axis

We focus on a set of hormones - LH, FSH, AMH, testosterone, sex hormone binding globulin (SHBG), estradiol, β-endorphins, oxytocin, kisspeptin, and activin/inhibin - that play central roles in orchestrating the female HPG axis. We excluded progesterone because the abnormalities of progesterone function in both conditions are complex and beyond the scope of this review; for example, anovulation in PCOS directly results in absence of progesterone production (see Kim, Kurita, & Bulun, 2013; Li et al., 2014). Table 3.2 summarizes the contrasting hormonal profiles between women with endometriosis and women with PCOS.

LH and FSH

Women with PCOS demonstrate increased frequencies and amplitudes of GnRH and LH pulses, increased LH levels, reduced FSH and an increased LH to FSH ratio, and a reduced capacity to mount the LH surge that initiates ovulation (Chang & Cook-Andersen, 2014; Chen et al., 2015; Coyle & Campbell, 2019; McCartney & Campbell, 2020). The granulosa cells from small antral follicles of women with PCOS prematurely switch from FSH to LH responsiveness, as indicated by elevated LH receptor expression and reduced FSH receptor expression compared with unaffected women (Kanamarlapudi, Gordon, & López, 2016; Owens et al., 2019; Franks & Hardy, 2020). These altered LH-FSH dynamics, combined with elevated ovarian androgens, contribute to the follicular arrest, anovulation, and cyst formation characteristic of PCOS (Franks & Hardy, 2020).

Women with endometriosis demonstrate reduced LH levels, indicating a lower frequency of GnRH and LH pulses (Cahill, Wardle, Maile, et al., 1995; Cheesman et al., 1982; Tummon et al., 1988). Several studies report elevated FSH in women with endometriosis compared with unaffected women (de Carvalho et al., 2010; González-Fernandez et al., 2011; Romanski et al., 2019; Yoo et al., 2011), though a few studies found no differences (Cahill et al., 1995; Lima et al., 2006). Endometriosis can thus be characterized overall, in contrast to PCOS, as involving a reduced LH to FSH ratio (e.g. Li et al., 2019). The premature switch to LH responsiveness of PCOS granulosa cells

also contrasts with findings from endometriosis: women with endometriosis demonstrate lower concentrations of LH receptors in the ovarian follicles throughout the menstrual cycle (Kauppila, Rajaniemi, & Rönnberg, 1982; Rönnberg, Kauppila, & Rajaniemi, 1984;) and their cycles involve longer follicular phases marked by delayed surges of LH (Cahill et al., 1995).

Table 3.2 Comparison of hormonal profiles between endometriosis and PCOS

Hormone	Relevant Functions	Activity, level in endometriosis relative to controls	Activity, level in PCOS relative to controls
Luteinizing hormone	Pituitary hormone that stimulates ovulation & corpus luteum development (Jeong & Kaiser, 2006)	Decreased, two surges	Increased, absent surge
Follicle stimulating hormone	Pituitary hormone that stimulates follicular maturation & estrogen secretion (Jeong & Kaiser, 2006)	Increased	Decreased
Anti-Müllerian hormone	Secreted by granulosa cells of large pre-antral & small antral follicles, stimulates LH, inhibits FSH (Barbotin et al., 2019)	Decreased	Increased
Testosterone	Produced by ovarian theca cells, regulates folliculogenesis & decidualization (Couse et al., 2006; Gervásio et al., 2014; Gibson et al., 2016)	Decreased	Increased
Sex hormone binding globulin	Influences bioavailability of sex hormones (Goldštajn et al., 2016)	Increased	Decreased
Estradiol	Secreted by granulosa cells, regulates development of female sex characteristics & endometrial proliferation (Rajkovic et al., 2016)	Low-normal (serum), High in lesions	Normal-high (serum), No mid-cycle peak
β-endorphin	Pituitary-produced peptide that inhibits GnRH & ovulation (Sprouse-Blum et al., 2010; Plein et al.,2018)	Decreased	Increased
Oxytocin	Neurohormone released from posterior pituitary that regulates uterine peristalsis (Gimpl & Fahrenholz, 2001)	Increased	Decreased
Kisspeptin	Hypothalamic protein that initiates GnRH secretion (Skorupskaite et al., 2014)	Mixed	Increased
Activin	Ovarian cytokine that stimulates FSH, decreases LH (Seachrist & Keri, 2019)	Increased	Decreased
Inhibin	Ovarian cytokine that restrains activin (Seachrist & Keri, 2019)	Decreased	Increased

Menstrual cycles of women with endometriosis more frequently demonstrate two LH surges compared with the typical single surge recorded in control subjects (90% of endometriosis cycles showed biphasic LH surges in Cheeseman et al., 1982, and 17% in Vaughan Williams, Oak, & Elstein, 1986), which contrasts with the absence of an LH surge, and corresponding anovulation, found in PCOS. Taken together, this evidence shows that endometriosis and PCOS exhibit opposite deviations from unaffected women in patterns of LH and FSH production and effects.

Anti-Müllerian hormone (AMH)

AMH regulates sex-specific early development and mediates ovarian reserve (Barbotin et al., 2019; Lv et al., 2020). The characteristic arrest of antral follicular development in PCOS results in high AMH (Zhao et al., 2019). AMH levels are higher in anovulatory compared to ovulatory women with PCOS (Cimino et al., 2016), and also positively predict symptom severity, including hyperandrogenism and polycystic ovarian morphology (Garg & Tal, 2016; Sahmay et al., 2014).

Women with endometriosis demonstrate reduced serum AMH relative to control subjects (Dong et al., 2019; Kasapoglu et al., 2018; Muzii et al., 2018; Romanski et al., 2019; Sánchez-Ferrer et al., 2019; Shebl et al., 2009). Women with endometriosis treated with ovarian surgery demonstrate an especially steep decline in AMH levels, but women with endometriosis who do not undergo surgery also show accelerated declines in AMH levels relative to unaffected women (Goodman et al., 2016; Kasapoglu et al., 2018; Muzii et al., 2018; Romanski et al., 2019). AMH levels also decrease with increasing severity of endometriosis (Shebl et al., 2009). Endometriosis and PCOS are thus associated with opposite levels of AMH, which also reflect diametric patterns in ovarian aging and menopause onset, as described in more detail below.

Testosterone, sex hormone binding globulin (SHBG), and estradiol

Elevated ovarian androgen production is a core feature of PCOS and results in PCOS symptoms including hair loss, acne, oily skin, and accumulation of abdominal fat (Rosenfield & Ehrmann, 2016). Levels of SHBG, a protein that transports steroids in biologically inactive form, are reduced in PCOS, permitting higher levels of bioavailable androgens (Deswal, Yadav, & Dang, 2018). Elevated androgen production contributes to functional changes in the adipose tissue of women with PCOS, generating chronic low-

grade inflammation across multiple tissues (Cooke, Connaughton, Lyons et al., 2016; Fuertes-Martín, Moncayo, Insenser, et al., 2019).

Women with PCOS demonstrate normal or elevated levels of serum estradiol relative to controls (Kawwass et al., 2017; Laven et al., 2002), but they exhibit reduced ovarian aromatase activity with a corresponding decrease in the ovarian estrogen to testosterone ratio (Chen et al., 2015; Hunter & Sterrett, 2000; Jakimiuk et al., 1998; Kirilovas et al., 2006). Low FSH and epigenetic changes in regulatory regions of the aromatase gene CYP19A1 are associated with the aromatase deficiency and androgen excess in PCOS (Franks, Stark, & Hardy, 2008).

In contrast to PCOS, endometriosis is associated with increased SHBG and reduced serum and follicular testosterone (Frankfurter et al., 1997; Misao et al., 1995; Ono et al., 2014; Panidis et al., 1993). One study found that women with endometriosis had higher serum testosterone than unaffected controls, but this difference was not statistically significant (Evsen et al., 2014). More severe disease predicted lower follicular testosterone in another study (Pellicer et al., 1998). Following a period of gonadotropin suppression prior to *in vitro* fertilization (IVF), women with endometriosis showed reduced follicular testosterone relative to unaffected women (Rodríguez-Tárrega et al., 2020). Reduced testosterone, or hypoandrogenemia, is characteristic of chronic inflammatory diseases – a diverse range of conditions that involve long-term immune activation - as testosterone generally promotes energy storage and thus inhibits metabolically costly inflammation (Straub, 2014).

Endometriosis is described as an estrogen-dependent, chronic inflammatory disease (Bulun et al., 2019). Women with endometriosis show elevated estradiol in their menstrual blood, but not in their circulation, indicating high local estradiol production (Stilley et al., 2012; Takahashi, Nagata, & Kitao, 1989). Such increased local estradiol production appears to result from reduced expression of estrogen-metabolizing enzymes and increased aromatase expression (Attar & Bulun, 2006; Bulun et al., 2004; Hudelist et al., 2007; Huhtinen et al., 2012; Mori et al., 2019). The eutopic endometrium of women with endometriosis demonstrates significantly elevated aromatase activity compared with unaffected women (Bukulmez et al., 2008), and within affected women, aromatase expression positively predicts severity of dysmenorrhea (Maia, Haddad, & Casoy, 2012).

Some studies report lower levels of aromatase expression in the ovaries and endometrium of women with endometriosis compared with controls, indicating that aromatase expression varies with ethnicity, menstrual cycle phase, fertility status, and disease severity and subtype, as well as methodology used (Barcelos et al., 2015; Anupa et al., 2019). Findings from research with swine indicate that aromatase activity is influenced by prenatal testosterone exposure: when pregnant swine were treated with flutamide, an androgen receptor antagonist, their female offspring later demonstrated increased aromatase expression and elevated ovarian estradiol production (Grzesiak et al., 2012). Overall, endometriosis can be characterized as a condition involving increased estrogenic relative to androgenic activity, whereas PCOS is characterized as the reverse.

Endogenous opioid system

The endogenous opioid system is a sexually dimorphic modulator of the HPG axis that regulates immunity, analgesia, and stress (Eyvazzadeh, 2009; Böttcher et al., 2017). Females exhibit lower levels of β-endorphin and lower pain thresholds, relative to males (Wisenfeld-Hallin, 2005; Hashmi & Davis, 2014). Women with PCOS demonstrated higher β-endorphin than controls in one study (Kialka et al., 2016). Another study found no group differences in β-endorphin levels, but follicular β-endorphin positively predicted serum testosterone (Jaschke et al., 2018). Prenatal testosterone excess causes adult female rats to demonstrate male-typical responses to morphine (Cicero et al., 2002). In women with PCOS, opioids stimulate LH and insulin secretion, which increases androgen levels (Eyvazzadeh, 2009). Thus, hyperandrogenemia and hyperinsulinemia are worsened by an over-active opioid system and opioid antagonists improve PCOS symptoms, as described below.

Women with endometriosis, including women with pain-free endometriosis, demonstrate reduced β-endorphin compared with unaffected women (Vercellini et al., 1992). Women with endometriosis symptoms also show lower pain thresholds than women without endometriosis symptoms (Poli-Neto et al., 2019). Experimental induction of endometriosis in rats reduced opioid receptor expression by 20%, suggesting that the presence of endometriosis interferes with analgesia (Torres-Reveron et al., 2016). Thus, in contrast to PCOS, endometriosis appears to involve an under-active opioid system.

Oxytocin

Oxytocin, a neurohormone with diverse effects on the brain and body, regulates uterine peristalsis (Kunz & Leyendecker, 2002). Serum oxytocin and uterine peristalsis are elevated in women with endometriosis relative to controls (He et al., 2016; Leyendecker et al., 2004). Furthermore, endometrial oxytocin receptor expression is higher in affected women, and positively predicts dysmenorrhea (Harada, 2013; Huang et al., 2017). Serum oxytocin is, by contrast, reduced among women with PCOS compared to controls (Jahromi et al., 2018), and the observed frequency of uterine peristalsis is also reduced (Leonhardt et al., 2012). Type 2 diabetes and obesity, which frequently co-occur with PCOS (Diamanti-Kandarakis & Dunaif, 2012), are also associated with reduced serum oxytocin (Qian et al., 2014; Yuan et al., 2016).

Kisspeptin

The peptide kisspeptin, primarily expressed in the hypothalamus, regulates GnRH secretion, sex steroid feedback, and puberty onset in both sexes (Skorupskaite, George, & Anderson, 2014). Serum kisspeptin is higher in patients with PCOS than in control individuals across 12 studies (Tang et al., 2019), and its concentration is positively correlated with levels of free testosterone (Chen et al., 2010; Ibrahim, Omer, & Fattah, 2020). Given the stimulating effect of kisspeptin on GnRH neurons, evidence for elevated kisspeptin in women with PCOS fits with findings of higher-frequency GnRH and LH pulses in affected women.

One study found lower levels of kisspeptin in endometrial stroma among patients with endometriosis than in controls (Abdelkareem et al., 2020), and another study found no difference between groups (Timologou et al., 2016). To the best of our knowledge, there are no data on serum kisspeptin in women with endometriosis, but under the diametric hypothesis, lower serum kisspeptin, with corresponding reductions in GnRH and LH secretion, is expected.

Activin and inhibin

Activin and inhibin are protein complexes with opposite biological effects: activin contributes to menstrual cycle regulation through stimulating FSH production and decreasing testosterone, while inhibin reduces FSH synthesis and secretion (Seachrist & Keri, 2019). Women with endometriosis demonstrate higher levels of activin than

unaffected controls (Cahill & Hull 2000; Rombauts et al., 2006; Reis et al., 2012) and giving activin to mice promotes endometriotic lesion growth (Kasai et al., 2019). Conversely, women with PCOS are characterized by lower activin (Norman et al., 2001; Eldar-Geva et al., 2001) and higher inhibin (Tsigkou et al., 2008; Babcová et al., 2015), compared with controls. Taken together, these findings indicate that endometriosis and PCOS are characterized by opposite alterations to key hormones that regulate the female HPG axis.

3.4.3. Endometriosis and PCOS demonstrate opposite alterations to reproductive physiological processes

Given the roles of the HPG axis and its associated hormones in orchestrating reproductive functions including follicular maturation, ovulation, menstrual cycling, and uterine preparation for implantation, it follows from the diametric hypothesis that endometriosis and PCOS will involve opposite alterations in these reproductive physiological functions.

Folliculogenesis

High ovarian testosterone promotes early follicular growth, mediating the recruitment of follicles from the primordial stage to the small, pre-antral stage, and contributing to elevated antral follicle count, follicular arrest, anovulation, and the cyst formation characteristic of PCOS (Astapova et al., 2019). Women with PCOS thus demonstrate a slower transition from the primordial reserve to the dynamic reserve, with stalled development at the antral stage (Monniaux et al., 2014).

Lower testosterone in women with endometriosis shows evidence of contributing to a faster pace of follicular recruitment and death, across several studies. In ovaries affected by endometriosis, a higher proportion of primordial follicles are recruited into the growing pool and a greater number of maturing follicles degenerate, resulting in quicker depletion of ovarian reserve (Kitajima et al., 2014; Takeuchi et al., 2019). Women with endometriosis have fewer pre-ovulatory follicles as well as smaller follicles, relative to unaffected women (Stilley et al., 2012; Garcia-Velasco, 1999). Low serum testosterone predicts elevated pro-apoptotic factors in the follicular fluid of women with endometriosis, which increase follicular atresia (Ono et al., 2014). These findings are consistent with results from swine, in which female offspring of flutamide-treated mothers demonstrate

fewer follicles, greater activation of primordial follicles, and more apoptotic cells (Knapczyk-Stwora et al., 2013; Knapczyk-Stwora et al., 2019). These contrasting patterns of folliculogenesis help to account for early menopause in endometriosis and later menopause in PCOS, as discussed below.

Diametric dynamics of folliculogenesis are also observable in settings of assisted reproduction. As part of IVF, women receive doses of synthetic gonadotropins to stimulate their ovaries to rapidly mature several oocytes for harvest and fertilization (Siristatidis et al., 2012). During ovarian stimulation, women with endometriosis require higher doses of gonadotropin and produce fewer mature oocytes compared to infertile women without endometriosis (González-Fernandez et al., 2011, Al-Azemi et al., 2000; Muteshi et al., 2018; Bourdon et al., 2018). Furthermore, correlates of endometriosis, including low LH to FSH ratios, short AGD, and early menarche, predict poor response to ovarian stimulation in women without endometriosis (Prasad, Gupta, & Divya, 2013; Shrim et al., 2002; Kofinas & Elias, 2014; Fabregues, Peñarrubia, & Carmona, 2018; Sadrzadeh et al., 2003).

In contrast to women with endometriosis, women with PCOS require lower than typical doses of gonadotropin in IVF treatment, and produce more mature oocytes (González-Fernandez et al., 2011). PCOS is also associated with an increased risk of ovarian hyperstimulation syndrome, a serious condition resulting from supraphysiologic levels of gonadotropins (Kumar et al., 2011; Tummon et al., 2005), whereas endometriosis involves a decreased risk of this syndrome (Luke et al., 2010). In regularly menstruating women without endometriosis or PCOS, serum testosterone levels positively predict number of follicles and oocytes retrieved (Xiao et al., 2016; Sun et al., 2014), and women with higher serum testosterone require less FSH and a shorter duration of ovarian stimulation (Frattarelli & Peterson, 2004). Furthermore, giving testosterone to poor gonadotropin responders (who overlap with endometriosis in having low LH to FSH and short AGDs) increases retrieved oocytes and improves IVF success (Bosdou et al., 2012; Noventa et al., 2019; Luo et al 2014; but not in Sunkara, Pundir, & Khalaf, 2011).

These findings indicate that women with PCOS and women with endometriosis demonstrate opposite responses to controlled ovarian stimulation, which can be

understood in the context of diametric patterns of ovarian androgens and folliculogenesis.

Menstrual cycles

Women with PCOS demonstrate lengthened menstrual cycles, due to anovulation, absent luteal progesterone, and interrupted negative feedback on gonadotropin secretion (Franks & Hardy, 2020). Women with endometriosis, by contrast, demonstrate shorter menstrual cycles relative to unaffected women (Arumugam & Lim, 1997; Wei et al., 2016; Yasui et al., 2015). Endometriosis also involves an apparent elevated incidence of releasing two eggs due to biphasic LH surges, as described above. Female rodents prenatally exposed to low testosterone also demonstrate shorter estrus cycles, as well as higher rates of conception (Table 3.3).

Decidualization

Decidualization, the collective biochemical and morphological changes to the endometrium that prepare it for implantation (Okada, Tsuzuki, & Murata, 2018), is dysregulated in both endometriosis and PCOS. Aspects of decidualization in endometriosis can be characterized as over-expressed. Women with endometriosis demonstrate more mobile endometrial stromal cells, higher numbers of uterine natural killer cells, reduced regulation over endometrial invasion, as well as up-regulated angiogenesis, pro-inflammatory cytokine expression, and oxidative stress (Gellersen & Brosens, 2014; Brosens, Brosens, & Benagiano, 2012; Lessey, Lebovic, & Taylor, 2013; Xavier et al., 2005; Matteo et al., 2017; Sharpe-Timms, 2001; Soares et al., 2012). Indeed, Somigliana, Vigano, and Vignali (1999) hypothesized that immunological alterations to the endometria and other tissues of women with endometriosis promote excellent endometrial receptivity, in the absence of severe effects from endometriosis such as adhesions and anatomical obstructions. Furthermore, these alterations to decidualization contribute directly to the establishment and growth of ectopic endometrial tissue, the primary hallmark of this disorder (Patel et al., 2017).

Table 3.3. Comparison of reproductive traits between female rodents differing in intrauterine testosterone exposure (0M females exposed to lower testosterone; 2M females exposed to higher testosterone), and women with endometriosis compared to PCOS

Trait	Rodents	References	Women	References
Anogenital distance (AGD)	Lower in 0M females than in 2M females	(vom Saal & Bronson, 1978; vom Saal et al., 1990; Keisler et al., 1991; Clemens et al., 1978;Zehr et al., 2001)	Lower in endometriosis females than in controls Higher in PCOS females than in controls	(see Table 3.1 references)
Timing, onset of estrus, menarche	Earlier in 0M females than in 2M females	(vom Saal, 1989; Clark & Galef, 1998; vom Saal, 1981)	Earlier in endometriosis females than in controls Later in PCOS females of normal BMI than in controls	(Nnoaham et al., 2012; Day et al., 2015) (Welt & Carmina, 2013; Carroll et al., 2012; Sadrzadeh et al., 2003)
Estrus, menstrual cycle duration	Shorter in 0M females than in 2M females	(vom Saal, 1989; Clark & Galef, 1998; vom Saal, 1981; vom Saal & Bronson, 1980b)	Shorter in endometriosis females than in controls Longer, irregular in PCOS females than in controls	(Arumugam & Lim, 1997; Wei et al., 2016; Yasui et al., 2015) (Franks & Hardy, 2020)
Fertility & fecundity measures	Higher in 0M females than in 2M females	(Clark & Galef, 1990; Drickamer et al., 2001; Drickamer, 1996)	Reduced in endometriosis and PCOS (as diseases) 0M female twins have higher fecundity than 1M female twins Endometriosis associated with traits linked to higher fertility (low WHR, BMI)	(Bulun et al., 2019; Rosenfield & Ehrmann, 2016) (Bütikofer et al., 2019, Lummaa et al., 2007) (see Table 3.1 references)

Women with PCOS, in contrast to those with endometriosis, demonstrate incomplete and delayed decidualization (Younas et al., 2019). Genes involved in adhesion, invasion, and tissue remodeling are downregulated in endometrium of women with PCOS, causing reduced trophoblast invasion which contributes to increased rates of pre-eclampsia and early pregnancy loss (Brosens & Benagiano, 2015; Piltonen et al., 2015). Women with PCOS also demonstrate reduced numbers of uterine natural killer cells (Matteo, Serviddio, Massenzio, et al., 2010). Treatment with metformin, a drug prescribed for diabetes as well as PCOS, improves markers of endometrial receptivity in women with PCOS, including increased uterine blood flow (Palomba et al., 2006). Recent research with a hyperandrogenic mouse model showed that angiogenesis and uterine natural killer cells are increased with flutamide treatment, demonstrating that elevated testosterone levels inhibit decidualization (Gong et al., 2019).

To summarize, women with endometriosis demonstrate shorter menstrual cycles with preserved or even increased ovulatory rates, faster testosterone-mediated depletion of ovarian reserve, poor response to exogenous ovulatory stimulation, and exaggerated aspects of decidualization. Women with PCOS demonstrate longer menstrual cycles with infrequent or absent ovulation, slower testosterone-mediated depletion of ovarian reserve, strong response to ovarian stimulation, and reduced aspects of decidualization. These opposite sets of alterations from typical HPG functioning and associated hormonal activity contribute directly to the symptoms and fertility reductions of both conditions.

3.4.4. Endometriosis and PCOS are associated with opposite morphological traits

Testosterone and estradiol play important roles in shaping sexually dimorphic characteristics including body size and shape (e.g. Mondragón-Ceballos et al., 2015). In this context, PCOS is associated with morphological traits indicating elevated testosterone, and lower estrogen-to-testosterone ratios, including higher body mass index (BMI) and higher waist-to-hip ratio (WHR), which are driven by increased abdominal adiposity and higher muscle mass (Table 3.1).

In contrast to PCOS, women with endometriosis demonstrate physical attributes associated with lower testosterone, higher estrogen, or both, including lower BMI, lower

WHR, reduced abdominal fat, lower muscle mass, and a gynoid pattern of fat distribution on the hips and buttocks (Table 3.1).

In humans, lower WHR and lower BMI have been associated, across multiple studies including cross-cultural analysis, with measures of higher female 'attractiveness' to males, and with higher fecundity or reproductive value (Weeden & Sabini, 2005; Cloud & Perilloux, 2014; Andrews et al., 2017). Among mice, rabbits, and gerbils, 0M females (that developed under lower prenatal testosterone) demonstrate higher attractiveness to males than 2M females, across multiple studies employing a range of mate choice paradigms (vom Saal & Bronson, 1978; vom Saal & Bronson, 1980a; Clark & Galef, 1998; Rines & vom Saal, 1984). For example, odors of female rabbits with shorter AGDs elicit a stronger mating response from males, and these females produce larger, heavier litters (Bánszegi et al., 2012). These findings suggest that, among humans as well as non-human mammals (Table 3.3), females exposed to low testosterone in early development demonstrate phenotypic attributes that signal high fertility and reproductive value.

3.4.5. Endometriosis and PCOS are associated with opposite life history traits

The HPG axis proximately instantiates life history decision-making, integrating bodily information with environmental cues to coordinate the development and expression of key life history events such as onset of puberty and reproductive senescence (Segner, Kemenade, & Chadzinska, 2017).

Women with endometriosis show slightly but significantly earlier ages at menarche relative to unaffected women (≤ 12 years; Table 3.3). Women with PCOS demonstrate the opposite pattern: young women of normal weight who later develop PCOS are more likely to have had delayed or absent menarche (≥ 16 years; Table 3.3). Women with PCOS who reported themselves as overweight during menarche onset were more likely to have reported younger age at menarche (Welt & Carmina, 2013). This pattern is consistent with results from animal research: 0M females mature, mate, and conceive at earlier ages than 2M females (Table 3.3). Earlier-maturing female gerbils are also more fecund, birthing more litters with more young per litter (Clark & Galef, 1998).

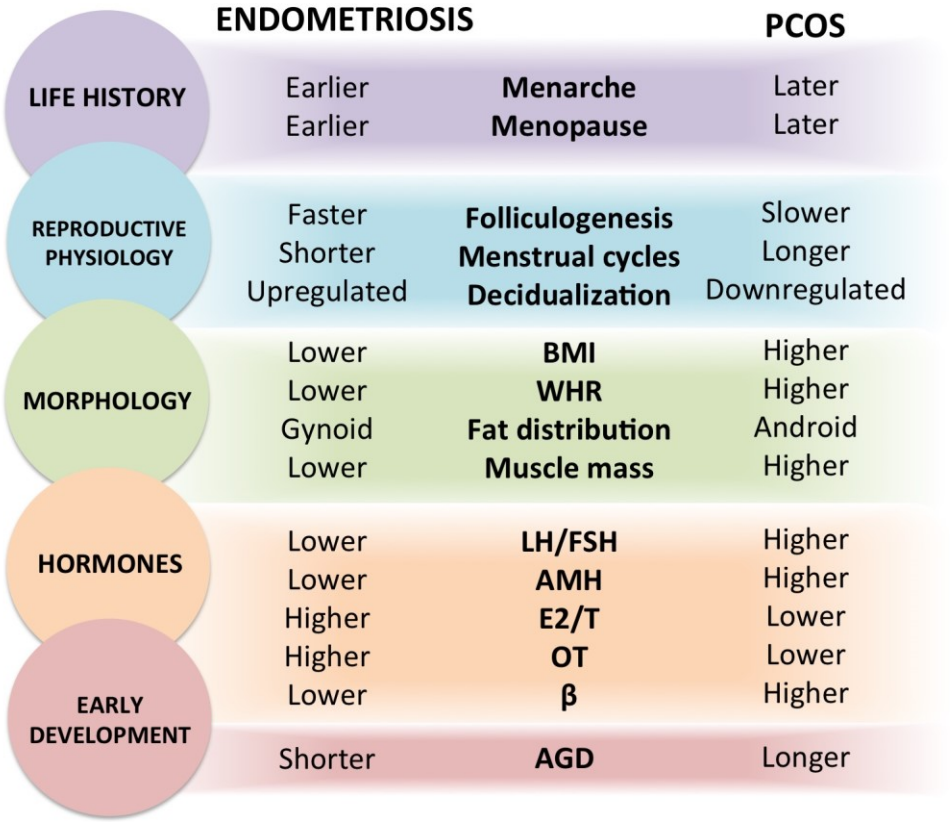
Reproductive senescence also shows opposite patterns between the two conditions. Women with endometriosis reach menopause at significantly earlier ages than unaffected women (Pokoradi, Iversen, & Hannaford, 2011; Yasui et al., 2011), whereas women with PCOS reach menopause significantly later than unaffected women (Forslund et al., 2019; Tehrani et al., 2010; Minooee et al., 2018, but not in Schmidt et al., 2011).

The two conditions also demonstrate diametric associations with multiple proxies of ovarian reserve. Compared to unaffected women, women with PCOS demonstrate elevated numbers of immature follicles, and their pool of potential oocytes declines more slowly through time, as reflected by a slower reduction in AMH (Hudecova et al., 2009; Nikolaou & Gilling-Smith, 2004; Mulders et al., 2004). Endometriosis, by contrast, is associated with lower ovarian reserve (Seyhan, Ata, & Ucu, 2015; Shah, 2013), increased primordial follicle recruitment (Takeuchi et al., 2019), fewer antral follicles (Muzii et al., 2018), and a steeper rate of decline in AMH (Kasapoglu et al., 2018).

The effects of low versus high prenatal testosterone exposure on several phenotypes, including life history traits, can usefully be compared between human women and non-human female mammals. Table 3.3 shows that low versus high prenatal testosterone exposure has consistent effects on female development and reproduction between rodents and humans.

Figure 3.1 summarizes the diametric phenotypes of endometriosis and PCOS, in the context of the diverse lines of evidence described above.

Figure 3.1 Summary of diametric phenotypes between endometriosis and PCOS



Diametric phenotypes between endometriosis and PCOS are evident across multiple categories, including early testosterone-mediated development (red), adult endocrinological activity (orange), body morphology (green), reproductive physiology (blue), and life history (purple). Abbreviations: body mass index (BMI); waist-to-hip ratio (WHR); luteinizing hormone relative to follicle stimulating hormone (LH/FSH); anti-Müllerian hormone (AMH); estradiol relative to testosterone (E2/T); oxytocin (OT); β-endorphin (β); and anogenital distance (AGD).

3.4.6. Endometriosis and PCOS rarely occur together

If endometriosis and PCOS are diametric disorders, then they should tend to not co-occur within individuals; thus the diametric hypothesis predicts that rates of endometriosis should be lower or non-existent in women with PCOS. This prediction needs to be evaluated with careful consideration of comparison groups, as even among women with no self-reported symptoms of endometriosis (pain, heavy bleeding, infertility), laparoscopic examination conducted for other reasons sometimes reveals evidence of endometriosis. To evaluate this prediction, we draw on data that compares

rates of discovered endometriosis between women with PCOS and women free of PCOS and endometriosis symptoms.

Moghadami-Tabrizi and colleagues (1998) compared PCOS patients to asymptomatic women (women undergoing tubal ligation who had no symptoms of PCOS or endometriosis) and found that the asymptomatic women had a significantly higher prevalence of endometriosis lesions (19.9%) than did the women with PCOS (7.3%); for both groups, the endometriosis was reported as minimal or mild. A meta-analysis of studies assessing the presence of endometriosis in women with PCOS undergoing ovarian drilling found that, overall, 7.7% of women with PCOS demonstrated evidence of endometriosis, all of which was minimal or mild (Hager et al., 2019).

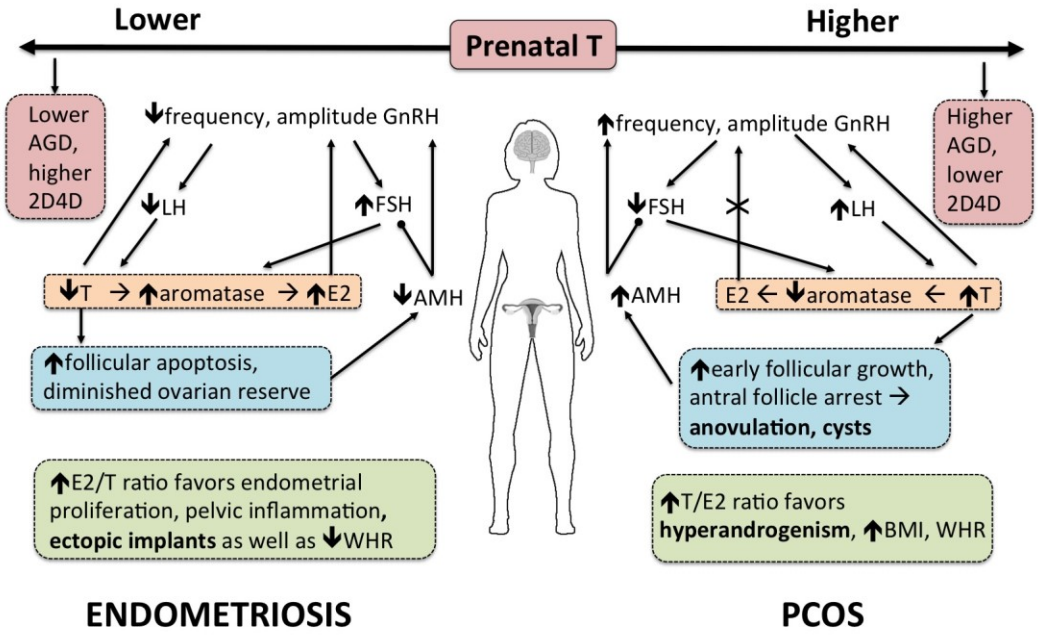
These rates of about 7-8% of asymptomatic endometriosis phenotypes in women with PCOS can be compared with results from studies that looked for evidence of asymptomatic endometriosis among women who were undergoing tubal ligation. These studies yielded rates of endometriosis that center around 19% (Tissot et al., 2017; Barbosa et al., 2009; Rawson, 1991). Holoch and colleagues (2014) reported high rates of endometriosis in women with PCOS (>70%), but the PCOS group was subject to ascertainment bias because the women were examined for endometriosis only if they self-reported pelvic pain and/or infertility. Taken together, these studies suggest that, among women without any clear symptoms of endometriosis (pain, heavy bleeding, infertility), the rate of this disorder as determined by laparoscopy is about one-half to one-third lower in women with PCOS than in women with no known reproductive issues.

3.5. Discussion

We have evaluated the hypothesis that endometriosis and PCOS represent opposite, extreme, and dysregulated manifestations of variation in female HPG axis development and functioning, with risk strongly modulated by levels of prenatal testosterone. The developmental and endocrine bases for the hypothesis are summarized in Figure 3.2. Whereas elevated prenatal testosterone is a well-established cause of PCOS (e.g. Abbott, Dumesic, & Levine, 2019; Filippou & Homburg, 2017), understanding endometriosis as a developmental disorder involving reduced prenatal testosterone exposure is a novel contribution with diverse clinical, research, and theoretical implications. Our review of evidence supports the hypothesis that

endometriosis and PCOS represent diametric disorders that reflect extreme expressions of evolutionary-ecological tradeoffs (Crespi & Go, 2005), proximately mediated by variation in prenatal development and HPG functioning across the female reproductive lifespan.

Figure 3.2 The diametric disorders hypothesis for endometriosis and PCOS



The diametric disorders hypothesis for endometriosis and PCOS proposes that opposite levels of prenatal testosterone exposure (low in endometriosis; high in PCOS) program the developing HPG axis, resulting in under-production (in endometriosis) and over-production (in PCOS) of ovarian testosterone relative to estradiol in adulthood. Pointed arrowheads indicate a stimulating effect (e.g. GnRH stimulates LH) and rounded arrowheads indicate an inhibitory effect (e.g. AMH inhibits FSH). The positive feedback effect of E2 on GnRH release is interrupted in PCOS, denoted by X. Altered testosterone to estradiol ratios in both conditions directly contribute to their symptoms (noted in bold). Abbreviations: Gonadotropin releasing hormone (GnRH); luteinizing hormone (LH); follicle stimulating hormone (FSH); testosterone (T); estradiol (E2); anti-Müllerian hormone (AMH); anogenital distance (AGD); second to fourth finger ratio (2D4D); waist-to-hip ratio (WHR); body mass index (BMI).

Multiple lines of evidence support the hypothesis that, in contrast to PCOS, endometriosis involves low prenatal testosterone: (1) women with endometriosis demonstrate significantly shorter AGDs than unaffected women; (2) female rodents naturally exposed to low prenatal testosterone demonstrate short AGDs, as well as earlier reproductive maturation and shorter estrus cycles, which are correlates and risk factors of endometriosis; (3) endometriosis symptoms (heavy, painful menstruation) are

associated with reduced prenatal testosterone, as indexed by digit ratio; (4) endometriosis involves a set of HPG alterations (low LH to FSH, low AMH, low ovarian T) that are opposite to the HPG alterations characteristic of PCOS that, from a large body of animal research, are known to be caused by prenatal testosterone excess; and (5) blocking androgen activity during fetal development increases ovarian estradiol production in swine, and elevated ovarian estradiol is a major proximate cause of endometriosis. These independent lines of evidence converge in revealing a causal role for low prenatal testosterone in the development of endometriosis.

Diverse evidence also indicates that low prenatal testosterone primes the adult HPG axis to under-produce ovarian testosterone, and that low adult testosterone contributes to endometriosis symptoms and correlates: (1) women with endometriosis demonstrate reduced levels of follicular and serum testosterone; (2) AGD is positively correlated with circulating testosterone in healthy women; (3) low serum testosterone in women with endometriosis increases the rate of follicular recruitment and atresia, contributing to diminished ovarian reserve and earlier menopause of affected women; (4) testosterone supplementation increases ovarian response to exogenous hormones; (5) chronic inflammatory diseases, a category to which endometriosis belongs, are characterized by hypoandrogenemia; and (6) women with endometriosis tend to demonstrate a suite of morphological phenotypes that centrally involve reduced testosterone relative to estradiol, including low BMI and WHR. Together, these lines of evidence support the diametric model's framing of core endometriosis symptoms and correlates as involving low ovarian and circulating testosterone, with developmental roots in low prenatal testosterone.

That *high* prenatal testosterone programs the adult female HPG axis to continually over-produce ovarian testosterone is well documented in humans and several animal models. How *low* prenatal testosterone impacts female HPG development and activity, and subsequent reproduction, has received significantly less research attention, perhaps due to conceptual biases in the literature towards higher, but not lower, testosterone being considered as physiologically and developmentally causal.

Accounts of endometriosis have largely focused on the role of estrogen, as estrogen proximately contributes to lesion growth through its proliferative and inflammatory effects on endometrial tissue. Such characterization of endometriosis as an

estrogen-dependent disease (e.g. Bulun et al., 2019) may have inadvertently overshadowed the role of testosterone in endometriosis etiology. For example, recent replicated findings of short AGD in women with endometriosis (Mendiola et al., 2016; Crestani et al., 2020; Peters et al., 2020) were, in each article, interpreted as indicative of an overly estrogenic prenatal environment. Estrogenic prenatal environments do decrease AGD (Stewart, Mattiske, & Andrew, 2018) and increase endometriosis risk (e.g. Missmer et al., 2004), so this interpretation is accurate but incomplete. Given that AGD is generally used as a proxy for prenatal testosterone exposure, and that AGD predicts adult testosterone levels but not estrogen (Eisenberg et al., 2012; Mira-Escolano et al., 2014), it is clearly important to address both estrogen and testosterone when investigating endometriosis etiology.

Positioning this expanded awareness of how estrogen and testosterone together mediate risk of female reproductive disorders in an evolutionary context provides productive avenues for further research. Given that estrogen and testosterone represent key female and male sex hormones, endometriosis and PCOS can be conceptualized as existing at opposite ends of a spectrum of variation in sexually dimorphic traits, within females (Dinsdale, Nepomnaschy, & Crespi, 2021). Traits typically observed in females relative to males, including short AGD, gynoid physique, low β-endorphin and testosterone, and elevated oxytocin, are thus especially highly expressed in women with endometriosis. In an evolutionary medical context, this suite of phenotypes may be framed as representing an extreme expression of female reproductive adaptations. Because prenatal testosterone plays a crucial role in mediating sex differentiation *in utero*, endometriosis may be fruitfully explored as involving an especially female-biased trajectory of reproductive development.

A second evolutionary context through which to understand the diametric relationship between endometriosis and PCOS is life history tradeoffs. Framing endometriosis and PCOS as opposite and extreme expressions of life history strategies is supported by the clear continuity of prenatal testosterone effects on reproductive life histories across females of multiple mammalian species (Table 3.3). Correlates of endometriosis, particularly earlier menarche and menopause and rapid menstrual cycling, indicate a life history strategy where early investment into reproduction is favoured. In both traditional and modern populations, younger age at menarche predicts

earlier first pregnancy as well as higher fecundability (Hochberg, Gawlik, & Walker, 2011; Guldbrandsen, Håkonsen, *Ernst et al.,* 2014). High investment into early reproduction is expected to entail survival costs, which should be greater in conditions of poor resource availability. Indeed, Lycett and colleagues (2000) reported a negative relationship between fecundity and longevity for women with low access to resources. Another study found that a faster pace of reproduction with higher parity resulted in higher mortality and poorer nutritional condition, though only in the short term (Gurven, Costa, Trumble et al., 2016).

PCOS, involving later menarche and menopause and extended or absent menstrual cycling, may represent a maladaptive extreme of a strategy where investment into maintenance and survival is favoured over reproductive effort, particularly in challenging environments (reviewed in Corbett & Morin-Papunen, 2013). Investment into visceral fat - which is elevated in lean as well as obese women with PCOS - appears to enhance health and survival in harsh conditions of low nutrition and high infection (West-Eberhard, 2019). Studies of mice indicate that, in environments with high population densities, females prenatally exposed to high testosterone may be more effective competitors for limited resources (vom Saal, 1980a). Higher prenatal testosterone exposure could thus be beneficial for females in environments where resource competition is high and traits such as increased robustness, muscularity, and dominance provide survival and competitive benefits. Contrasting PCOS and endometriosis as extreme expressions of life history strategies provides insights into the costs and benefits of prenatal testosterone exposure to female development and behaviour, an area that has received little attention thus far.

A central strength of the diametric hypothesis is that it is capable of unifying previous hypotheses for the causes of endometriosis. One widely accepted explanation for endometriosis is that, in some women, refluxed endometrial cells from menstruation are insufficiently cleared from the peritoneal cavity, and then implant and proliferate into lesions (Sampson, 1927). The diametric hypothesis addresses the puzzle of why, although 90% of women experience retrograde menstruation (Halme et al., 1984), only 5-10% of women develop endometriotic lesions: (1) low prenatal and postnatal testosterone contribute directly and indirectly to more menstruations and greater menstrual blood volume via early menarche, shorter menstrual cycles, and thicker

endometrial lining; (2) high local estradiol relative to testosterone increases inflammatory responses to ectopic tissue in women with endometriosis; and (3) elevated oxytocinergic activity increases uterine contractility, increasing the likelihood and volume of reflux menstruation.

Another important hypothesis for the etiology of endometriosis is based on inflammatory activation of developmentally mislocated stem cells, or Müllerian fragments (Sasson & Taylor, 2008; Russell, 1899). By the diametric model, such events are mediated by effects of prenatal testosterone on expression of reproductive developmental genes including HOXA10 (Cermik, Selam, & Taylor, 2003; He et al., 2018) as well as other genes involved in cell apoptosis, migration, and proliferation (Knapczyk-Stwora et al., 2019, Laganà et al., 2017).

The diametric disorders hypothesis for endometriosis and PCOS is subject to important caveats and limitations. There are research areas where existing evidence is limited or absent. For example, connections of AGD with testosterone and follicular count come from one dataset (e.g. Murcia Young Women's Study; Mendiola et al., 2012; Mira-Escolano et al., 2014) and thus require replication. More studies examining testosterone levels and correlations between testosterone levels and endometriosis symptoms and severity are also needed.

Evidence of endometriosis lesions in women with PCOS indicates that causes of endometriosis apart from prenatal testosterone exposure should also be considered. This co-occurrence is low, and such overlap might be explained in the following three ways. Firstly, endometriosis can be induced by treatments for PCOS (and vice versa) (Dinsdale, Nepomnaschy, & Crespi, 2021), which could account for some of the co-occurrence. Secondly, when endometriosis is discovered in women with PCOS, it is mild. Risk factors for endometriosis that are strongly linked to low prenatal testosterone, such as short AGD, are especially predictive of severe endometriosis. Mild endometriosis may be framed as a possible outcome of normal inflammation involved in female reproductive processes. An analogy to cancer can be applied here, whereby some people and families are especially prone to specific, aggressive kinds of cancer, but anyone can develop cancerous growths under certain environmental or lifestyle conditions. Environmental exposures (e.g. endocrine disrupting chemicals) can also dysregulate normal endocrine and inflammatory processes and may reduce the

threshold for endometriosis lesions in women who, under the diametric model, would be considered low risk for the disease. Thirdly, aspects of PCOS, such as high testosterone, could independently contribute to endometriosis lesions through increasing susceptibility to infection, which is a hypothesized proximate pathway whereby endometriosis lesions begin (García-Peñarrubia et al., 2020).

There are other examples of phenotypic similarity between PCOS and endometriosis, such as inflammation and progesterone resistance, but these appear to manifest differently and involve different causes (e.g. Li et al., 2014; Patel et al., 2017). Under the diametric hypothesis, areas of phenotypic overlap are expected to involve opposite proximate causes in the two conditions, but further study is required. A final limitation to consider is that, to the best of our knowledge, the effects of prenatal androgen deficiency have only been experimentally assessed in swine, whereas the effects of prenatal androgen excess on the developing female HPG axis are well characterized from experiments on diverse animal models. Future studies that experimentally analyze the proximate basis of endometriosis in prenatal development, coupled with work that focuses on the adaptive evolutionary tradeoffs and extremes involved in risks of endometriosis and PCOS, should provide substantial new insights into the causes and treatments of both disorders.

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Chapter 4.

Diagnosis, pelvic pain and medication mediate cognitive empathic abilities among women with endometriosis or PCOS

Natalie L. Dinsdale, Donna R. Chizen, & Bernard J. Crespi

4.1. Abstract

Endometriosis and polycystic ovary syndrome (PCOS) involve altered levels and activity of testosterone and oxytocin, two hormones that also centrally mediate human social cognition. We tested for effects of endometriosis or PCOS diagnosis, self-reported pelvic pain, depression levels, and medication use, on scores for the Reading the Mind in the Eyes task (RMET), a metric of social cognitive empathic abilities. Women with endometriosis showed lower scores on the RMET, compared to unaffected women and women with PCOS. However, among women with endometriosis, higher levels of pelvic pain and higher scores on an index of depression were associated with enhanced RMET performance. Among women with PCOS, medication with spironolactone, an androgen receptor antagonist, was associated with higher RMET scores, compared to women with PCOS who were not medicated or who were taking different medications. These results suggest that symptoms, hormonal correlates, and some treatments of PCOS and endometriosis mediate variation in cognitive empathy.

4.2. Introduction

Reproductive disorders exert substantial negative impacts on women's health, fertility, and quality of life through both physiological and psychological effects. Endometriosis and polycystic ovary syndrome (PCOS), the two most common female reproductive disorders, involve atypical hormonal profiles that contribute to problematic symptoms for affected women. Thus, endometriosis involves the proliferation and inflammation of endometrial or endometrial-like tissue beyond the boundaries of the uterus (Bulun et al., 2019), with pelvic pain, and risk for the disorder, linked to high levels of estrogen and oxytocin and low testosterone (Ono et al., 2014; He et al., 2016; Dinsdale & Crespi, 2017; Huang et al., 2017; Yarmolinskaya, Khobets, Tral et al., 2020; Dinsdale et al., 2021). By contrast, PCOS involves irregular, prolonged or absent ovulation, hirsutism, acne, weight gain, and polyfollicular ovaries, most of which are associated with relatively high levels of testosterone (Fauser et al., 2012; Rosenfield & Ehrmann, 2016), and treatments frequently involve drugs that reduce testosterone or block androgen activity (Rosenfield & Ehrmann, 2016; Goodman, Cobin, Futterweit, Glueck, et al., 2015). PCOS also shows evidence of reduced oxytocinergic activity that may mediate some of its effects (Jahromi et al., 2018).

In contrast to the endocrine-related differences between endometriosis and PCOS, both disorders involve heightened risks of depression and anxiety that derive from pain, concerns about fertility or attractiveness, and other factors (Facchin, Barbara, Saita et al., 2015; Deeks, Gibson-Helm, & Teede, 2010). These aversive psychological states are modulated in part by levels of hormones (e.g. Walf & Frye, 2006; Giltay et al., 2012), some of which are known to be dysregulated in these disorders.

Associations of endometriosis and PCOS with variation in hormonally mediated psychological phenotypes other than depression and anxiety remain largely unstudied. Cognitive empathy, the capacity to decode and understand the thoughts and emotions of others, and take their mental perspective, plays central roles in positive and efficacious human social cognition and interactions (Crespi, 2015; de Waal & Preston, 2017). Moreover, a suite of psychoendocrinological studies has demonstrated that cognitive empathic abilities tend to be decreased by the presence of relatively high levels of testosterone (and other pro-androgenic factors) (Domes et al., 2007; Khorashad et al.,

2018), and increased by relatively high levels of oxytocin (Riem et al., 2014; Schwaiger et al., 2019).

Taken together, these findings suggest that cognitive empathy may be enhanced among women with endometriosis, in association with low testosterone and high oxytocin, and reduced among women with PCOS, in association with high testosterone and low oxytocin. These simple predictions are, however, complicated by several factors, including: (1) associations of mild (but not severe) depression with enhanced cognitive empathic skills in women without reproductive disorders (Harkness, Sabbagh, Jacobson et al., 2005; Richman & Unoka, 2015); (2) a role for higher pain sensitivity and experience in enhancement of empathy, given, for example, that some analgesics can reduce empathic feelings (Mischkowski, Crocker, & Way, 2016); and (3) treatment of women affected by endometriosis or PCOS with therapeutic agents that alter levels of testosterone or oxytocin, including for example the androgen receptor antagonist spironolactone (Sirmans & Pate, 2013) or the synthetic androgen danazol (Selak et al., 2001).

In this study, a set of symptom-related factors, including diagnosis, pain levels, depression, and medications, was investigated to determine if and how they affect cognitive empathy abilities, assessed using the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001), among women with endometriosis or PCOS relative to controls. The main goals of the study were to: (1) provide data on cognitive empathy performance in women with endometriosis and women with PCOS, relative to unaffected women; (2) examine if and how pelvic pain and depression severity mediated cognitive empathy in women with these disorders; and (3) investigate possible effects of some commonly-used endometriosis and PCOS medications on cognitive empathy abilities.

4.3. Method

4.3.1. Recruitment and data collection

The recruitment materials invited women with endometriosis, PCOS, or no known gynecological diagnosis to participate in the online survey. Female participants were recruited through online advertising in endometriosis and PCOS support groups, emails to Saskatchewan-based pelvic pain physicians and support groups, as well as through

poster advertising on the University of Saskatchewan campus and online news feed. Following their completion of the online survey, participants were offered the opportunity to request an electronic gift card, which was emailed within 48 hours of their participation. In order to detect a mean difference in cognitive empathy scores of two points between groups with 80% power, a power analysis with $\alpha = 0.05$ determined that a minimum sample size of 50 participants per group was required. We aimed to recruit 100 women for each of the three study groups.

To join the study, all women needed to be between the ages of 18 and 35, not currently pregnant or breastfeeding, at least six months postpartum, and not have sustained any pelvic or abdominal injuries or surgeries in the past 6 months (excluding diagnostic laparoscopy). Women needed to have received either a diagnosis of PCOS or endometriosis (but not both), or have no known reproductive disorders.

If women met these criteria after their initial request to participate, they were sent a link to access the online survey, which was hosted on Survey Monkey. The survey included demographic questions, medical history questions, a pelvic pain questionnaire, and several psychological questionnaires, including a survey about depression and a cognitive empathy task, as described below.

4.3.2. Evaluation of diagnostic status

Confirming the diagnosis of endometriosis or PCOS is a complex task, so to increase our certainty that participants belonged to one of these groups, several questions were asked about their medical history. To confirm that females could confidently be assigned to the endometriosis group, participants needed to confirm that they had been diagnosed with endometriosis, and that the diagnosis had occurred following a laparoscopy. If women answered that a doctor told them they had endometriosis or suspected endometriosis but did not explicitly report that diagnosis had occurred via laparoscopy, they were excluded from the analyses.

To confirm that females could accurately be assigned to the PCOS group, women were asked specifically about their PCOS diagnosis, how it was made and who made it. They were also asked about each individual PCOS diagnostic criterion (menstrual periods > 35 days long; elevated androgens and/or hirsutism; ultrasound

confirmation of polycystic ovaries). If there was agreement between the two sets of questions, then the participant was included in the PCOS group. For example, if a woman reported that a doctor had diagnosed them with PCOS, and then they also reported hirsutism and confirmed polycystic ovaries or lengthened menstrual cycles, then the woman was assigned to the PCOS group. If they reported having a diagnosis of PCOS but answered 'no' to having lengthened menstrual cycles, hirsutism, or polycystic ovaries, they were excluded from analyses. Women reporting a diagnosis of both endometriosis and PCOS were also not included in the analyses.

4.3.3. Questionnaires

To measure cognitive empathy, participants completed the 'Reading the Mind in the Eyes' test (RMET) revised version developed by Baron-Cohen and colleagues (2001). The RMET assesses how accurately a person can infer emotions from looking at the eye region of faces, presented in photographs. This test is widely used in psychology and other disciplines, usually to assess differences in cognitive empathy across people with different psychological traits or psychiatric diagnoses. The test is composed of 36 pictures. The person in the photo is expressing an emotion and the participant is requested to select, from four choices, the word that best describes the emotional expression. A glossary is provided that defines the emotion word choices, in case a participant is not clear on a word's meaning; this glossary was available as a web link in our survey. Each correct RMET response is given one point, for a range of zero to 36 points.

The survey included Beck's Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996), a 21-item questionnaire that assesses the presence and severity of depression. Each item includes four statements and the participant is instructed to select the statements that best describes them. Statements indicating no depression (e.g. "I do not feel sad") are scored zero points, statements indicating extreme depression (e.g. "I am so sad and unhappy that I can't stand it") are given three points, and intermediate statements are scored one or two points, for a range of zero to 63 points.

The survey set also included questions about the intensity and frequency of the pelvic pain experienced by participants. This measure (see Appendix A) was generated with guidance from the publicly available Pelvic Pain Assessment Form from the

International Pelvic Pain Society (2008). This questionnaire included nine questions with four Likert-style response options, ranging from no pain to extreme pain. Responses indicating no pain or infrequent pain were given zero points and responses indicating extreme or constant pain were given three points, for a range of zero to 27 points.

Information was also requested concerning participant medication usage, given that medications can alter hormones and impact mood and cognition. Participants first answered yes or no to using medications, and if they answered yes, they were asked to list all medications in a blank field. All statistical analyses were done in R.

4.3.4. Ethical approval

The study was jointly approved by the Ethics boards at the University of Saskatchewan and Simon Fraser University (Permit Number 2017-0407).

4.4. Results

4.4.1. Subjects and demography

A total of 466 questionnaires were received. Of these, 75 participants could not be definitively assigned to a study group, 13 participants reported having both endometriosis and PCOS, and 36 participants left most of the questions incomplete. All of these participants were excluded from analyses. The final sample size was 342 women: 93 women with endometriosis, 123 women with PCOS, and 126 women with no known reproductive disorders as controls. Characteristics of the participants in each study group are summarized in Table 4.1.

There was a significant effect of group membership on age (F = 29.0, p < 0.001). Subsequent t-tests confirmed that the control group was significantly younger than both diagnostic groups (p < 0.001), and the PCOS group was significantly younger than the endometriosis group (t = 2.9, p < 0.01). Participant age was thus included in further analyses as a covariate.

Table 4.1 Participant characteristics by study group

Characteristic	Study group (*N* = 342)		
	Endometriosis (*n* = 93)	PCOS (*n* = 123)	Control (*n* = 126)
Age [M,(SD)]	**28.7(4.6)**	**26.8(4.6)**	**23.8(4.8)**
Ethnicity	78% Caucasian 3% Asian 3% Metis or Indigenous 3% Mixed 2% Hispanic 1% Black 10% other/not disclosed	69% Caucasian 7% Asian 7% Mixed 5% Hispanic 2% Black 2% Metis or Indigenous 8% other/not disclosed	65% Caucasian 13% Asian 7% Metis or Indigenous 6% mixed 4% Latin 5% other/not disclosed
Taking one or more medication [*n*, (%)]	66 (71%)	90 (73.1%)	(81) 64.3%

4.4.2. RMET, BDI, and pelvic pain

Means and standard deviations for RMET, BDI, and pelvic pain scores by study group are presented in Table 4.2. To examine the main prediction, an ANOVA was performed to test for group differences in RMET scores. There was a significant effect of study group on RMET scores: subsequent t-tests indicated that women with endometriosis scored significantly lower than controls (t = -2.5, p = 0.01) and lower than women with PCOS (t = -2.9, p = 0.005). There was no difference in mean RMET scores between women with PCOS and control women (t = 0.38, p = 0.7). RMET scores were not affected by age in an ANCOVA (p = 0.24).

Table 4.2 Mean scores and standard deviations for cognitive empathy, depression, and pelvic pain for each study group

Measure	Endometriosis (*n* = 93)	PCOS (*n* = 123)	Control (*n* = 126)
RMET	24.4 (6.4)	26.8 (3.6)	26.6 (4.9)
BDI	18.1 (9.4)	18.7 (9.7)	11.3 (8.2)
Pelvic pain	16.3 (5.2)	8.8 (4.3)	6.5 (3.6)

There was also a significant effect of study group on BDI Depression scores (F = 24, p < 0.0001). Women with endometriosis (t = 4.96, p < 0.0001) as well as women with PCOS (t = 6.1, p < 0.0001) had significantly higher BDI scores than control women. Mean BDI scores did not differ between the two diagnostic groups (t = -0.38, p = 0.7). Age had no effect on BDI scores (p = 0.5).

Levels of pelvic pain were significantly different between the three study groups (F = 133.6, p < 0.0001) and also varied with participant age (F = 14.1, p = 0.0002). As expected, women with endometriosis reported significantly higher levels of pelvic pain compared to controls (t = 15.1, p < 0.00001) and compared to women with PCOS (t = 11.0, p < 0.00001). Pelvic pain scores of women with PCOS were significantly higher than those of control women (t = 4.36, p < 0.001). Correlation tests demonstrated that younger age weakly and non-significantly predicted higher levels of pelvic pain in the diagnostic study groups only (endometriosis: r = -0.16, p = 0.13; PCOS: r = -0.17, p = 0.07).

Pelvic pain severity significantly and positively predicted BDI scores in the whole sample (r = 0.44, p < 0.00001). The severity of pelvic pain explained 28% of variation in BDI scores for the endometriosis group, 20% in the PCOS group, and 8% in the control group.

4.4.3. Pelvic pain, depression and diagnosis in relation to RMET

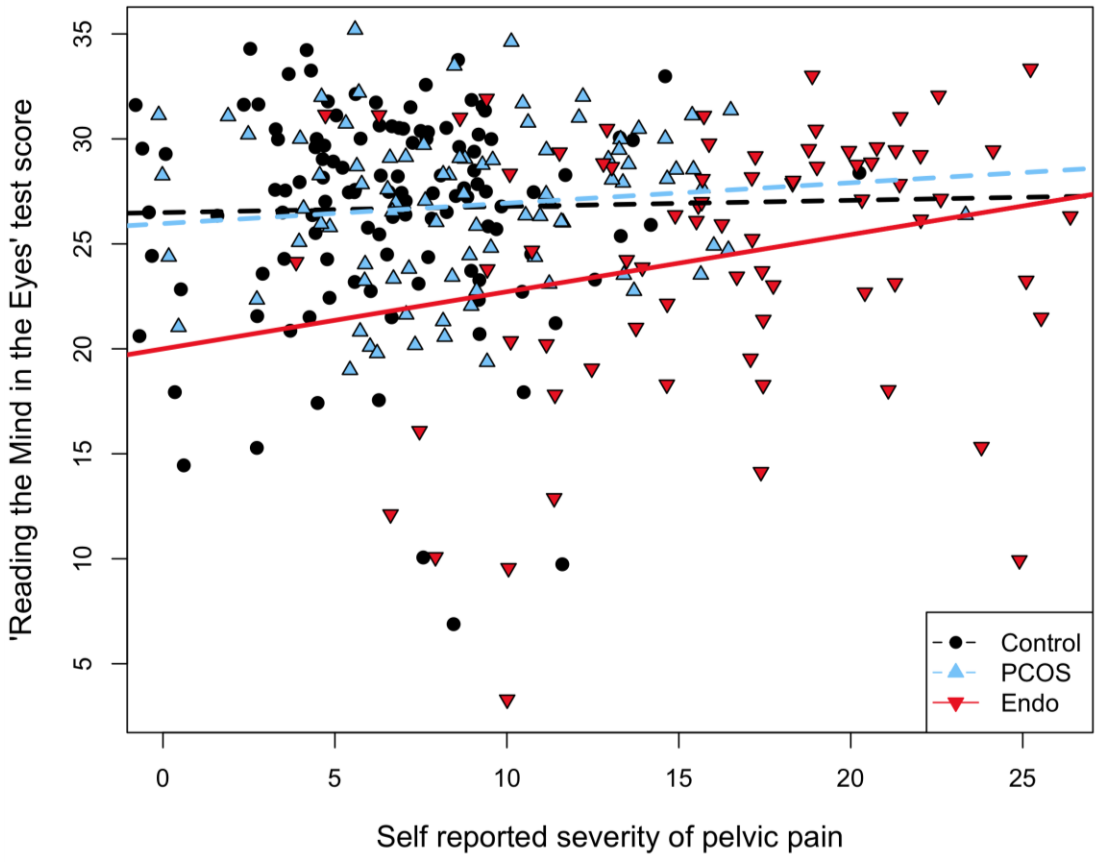
To investigate if and how RMET scores were associated with pelvic pain and depression (BDI scores) within and among study groups, pelvic pain, BDI scores, and study group were entered as predictor variables into a multiple linear regression model with RMET scores as the dependent variable. The fit of the linear model (rmet ~ pain* depression* group) was assessed using the aov function in R.

Both group (F = 5.8, p = 0.003) and pelvic pain (F = 4.6, p = 0.03) emerged as significant main predictors of RMET scores. There was a two-way interaction between study group and BDI scores (F = 3.8, p = 0.02) and a three-way interaction between study group, BDI score, and pelvic pain (F = 11.7, p < 0.0001). This model was a significant predictor of RMET scores (F = 4.58, p < 0.0001), explaining 13% of variation

in RMET scores. By contrast, regression models including BDI and group, or pelvic pain and group, explained 5.6% and 4.7% of variation in RMET scores, respectively.

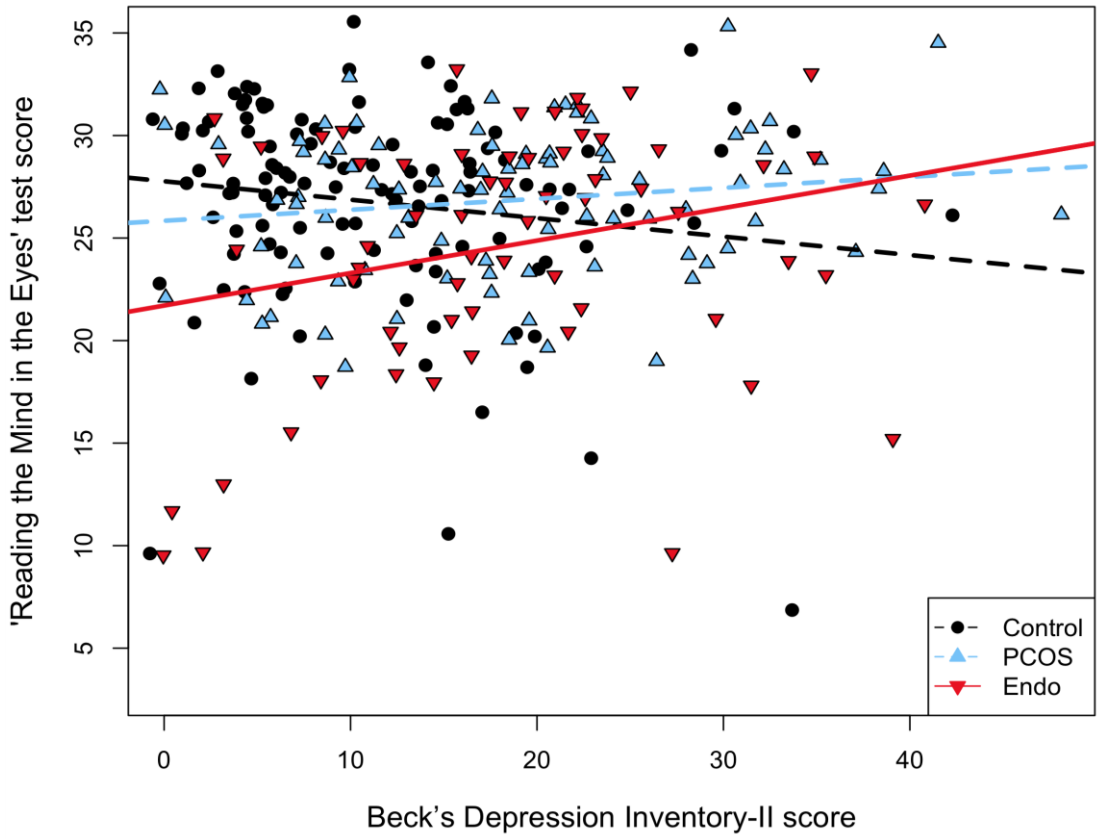
To further examine how interactions between depression, pelvic pain, and study group affected RMET performance, correlations were examined between pelvic pain and RMET, and BDI and RMET, within each study group (Figures 4.1 and 4.2). For women with endometriosis, pelvic pain (r = 0.23, p = 0.05) and BDI (r = 0.26, p = 0.04) were both significantly correlated with RMET, such that more severe pelvic pain and depression were associated with better performance on the RMET.

Figure 4.1 Pelvic pain positively predicted RMET scores in women with endometriosis



Pelvic pain positively predicted RMET scores in women with endometriosis (red solid line, r = 0.23, p = 0.05). There was no significant linear relationship (dashed lines) between pelvic pain and RMET scores in women with PCOS (blue, p = 0.28) or in controls (black, p = 0.82).

Figure 4.2 BDI scores significantly and positively predicted RMET scores in women with endometriosis



BDI scores significantly and positively predicted RMET scores in women with endometriosis (red solid line; r = 0.26, p = 0.04). BDI scores showed a non-significant trend toward negatively predicting RMET scores in control women (black dashed line; r = -0.15, p = 0.10). There was no correlation between BDI and RMET scores in women with PCOS (blue dashed line; r = 0.15, p = 0.16).

4.4.4. Medications and RMET performance

Based on the self-reported medications listed by participants, medications were grouped into the following categories: birth control; psychiatric medications; pain medications; spironolactone; metformin; progesterone medications; and all other medications. Table 4.3 provides a summary of medication usage by category for each study group.

Two categories of medication are directly relevant to empathy in their effects. First, pain sensitivity is known to be positively associated with levels of emotional empathy (Ren et al., 2020), and some pain medications have been shown to affect aspects of empathy in healthy adults (Mischkowski et al., 2016, 2019). These findings

suggest that levels of self-reported pain, and pain medications, may be associated with RMET performance.

Table 4.3 Number and percentage of participants taking different types of medication within each study group

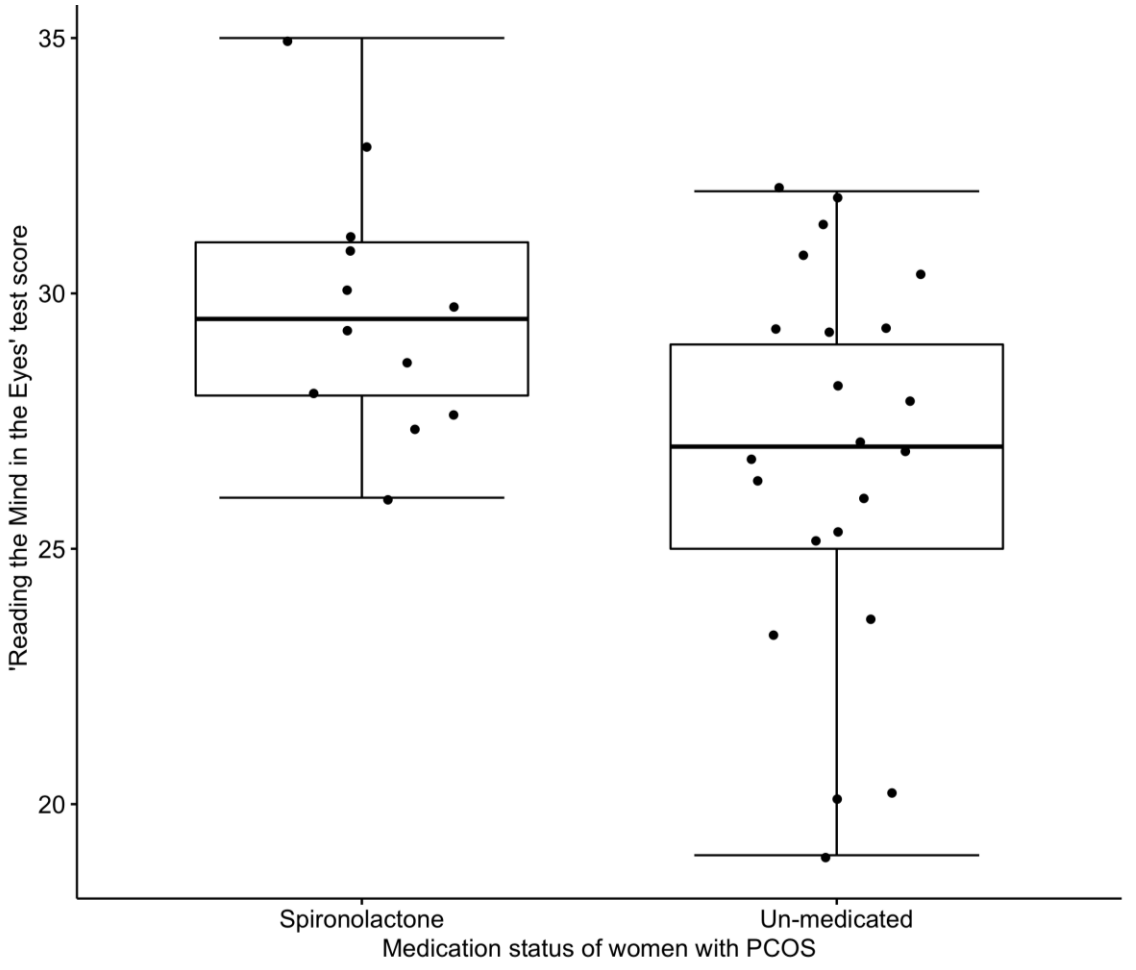
Medication Type	Endometriosis (*n* = 93)	PCOS (*n* = 123)	Control (*n* = 126)
Birth control (pill, injection, nuvaring, hormonal IUDS)	39 (41.9%)	54 (43.9%)	63 (50%)
Psychiatric	23 (24.7%)	20 (16.2%)	23(18.3%)
Pain	20 (21.5%)	1 (<1%)	2 (<1%)
Spironolactone or spirolactanone	0	15 (12.2%)	1 (<1%)
Metformin	0	29 (23.6%)	2 (<1%)
Progesterone (Provera, Visanne)	12 (23.6%)	3 (2.4%)	1 (<1%)
Other (allergy, gastrointestinal, migraine, thyroid, weight management, diabetes)	28 (30.1%)	32 (26%)	29 (23%)
None	27 (29%)	33 (26.8%)	45 (35.7%)

Second, higher levels of testosterone have been linked with reduced empathy, including RMET performance (Van Honk et al., 2011; Khorashad et al., 2018). Many women with PCOS use drugs that reduce testosterone levels and expression of testosterone-mediated symptoms, such as hirsutism and acne. These findings suggest that medications that reduce testosterone levels and activity, such as spironolactone, may influence RMET scores.

To examine the effects of pain medication on cognitive empathy, RMET scores of women with endometriosis taking pain medication were compared to scores of unmedicated (taking no medications) women with endometriosis. The women on pain medication may also be on other forms of medication, as our sample of women with endometriosis only taking pain medication was too small for among-group comparisons. Women with endometriosis taking pain medications performed significantly better on the RMET compared with unmedicated women with endometriosis (t = -2.1, p < 0.05). Women with endometriosis currently taking pain medications also reported significantly higher levels of pelvic pain compared to unmedicated women (women taking no medications) with endometriosis (t = 3.9, p < 0.001). There was no difference in RMET scores between women with endometriosis taking pain medication compared to affected women not taking pain medication (but taking other medications).

To examine the effects of spironolactone on cognitive empathy, RMET scores of women with PCOS taking spironolactone (n = 12) were compared to scores of unmedicated women with PCOS (n = 23). Women with PCOS currently taking spironolactone performed significantly better on the RMET than did unmedicated women with PCOS (Figure 4.3; t = 2.78, p < 0.01). For this test, it is important to note that women on spironolactone may also be taking other medications and that sample sizes for this analysis differ from the medication numbers in Table 4.3 because some women did not complete the entire RMET and could not be included in this analysis. Women with PCOS currently taking spironolactone also had higher scores on the RMET than did women with PCOS on other medications but not spironolactone (t = 3.93, p < 0.001).

Figure 4.3 Boxplots including error bars comparing RMET scores of women with PCOS currently taking spironolactone (*n* = 12) and un-medicated women with PCOS (n = 23). Each point represents one individual.



4.5. Discussion

This study investigated how women with endometriosis or PCOS perform on the RMET, a paradigmatic test of cognitive empathy. The main findings are threefold. First, women with endometriosis demonstrated lower scores on the RMET compared to both unaffected women and women with PCOS. Second, among women with endometriosis, higher levels of pelvic pain and higher scores on an index of depression were associated with better RMET performance. Third, women with PCOS taking spironolactone demonstrated significantly enhanced RMET performance compared to women with PCOS who were not medicated or who were taking different medications.

Endometriosis has been associated with higher oxytocin and lower testosterone (reviewed in Dinsdale & Crespi, 2021), so it may be expected that women with this disorder would score higher on the RMET than unaffected women, given that previous studies show that RMET scores are increased by lower testosterone and higher oxytocin in healthy individuals (Riem et al., 2014; Schwaiger et al., 2019). That women with endometriosis scored lower, on average, on the RMET compared with controls and women with PCOS is thus unexpected, although broadly consistent with other studies that report reduced RMET scores, compared to controls, in adults with chronic pain conditions including irritable bowel disease (Agostini et al., 2019), fibromyalgia (Inanc et al., 2019), and complex regional pain syndrome (Shin et al., 2013). Taken together, these findings suggest that chronic pain conditions may generally be associated with reduced cognitive empathy, for reasons that require further study.

However, in our study, higher pelvic pain as well as higher depression predicted better RMET performance in the endometriosis group only. A positive effect of pain on cognitive empathy skill among women with endometriosis thus appears to be a distinctive finding in the broader context of chronic pain research. For example, in men with complex regional pain syndrome, higher pain predicted worse RMET performance (Shin et al., 2013), severity of irritable bowel disease negatively predicted RMET scores in both sexes (Agostini et al., 2019), and in women with fibromyalgia, there was no relationship between pain and RMET scores (Di Tella et al., 2015). The positive relationship between pelvic pain severity and cognitive empathy performance reported here will require replication to assess its accuracy and to determine if it is indeed specific

to endometriosis. One possible explanation for specificity to endometriosis is that increased pelvic pain intensity in this disorder may be associated with higher oxytocinergic activity (which stimulates more intense and painful menstrual contractions) (reviewed in Dinsdale & Crespi, 2017), and lower testosterone (which increases pain sensitivity) (reviewed in Dinsdale et al. 2021), both of which could contribute to higher RMET scores. Indeed, Yarmolinskaya and colleagues (2020) reported that compared to unaffected women, women with endometriosis had higher blood oxytocin, and that blood oxytocin levels positively predicted the intensity of pelvic pain.

The observed positive association of BDI depression scores with RMET scores was specific to the endometriosis group. Severe and chronic pelvic pain predicts depression, regardless of the disease involved (Peveler et al., 1995), and women with painful endometriosis are significantly more likely to exhibit depressive symptoms than women with pain-free endometriosis (Lorençatto et al., 2006). Pelvic pain has been positively associated with depression in women with endometriosis (Brookes et al., 2020; Warzecha et al., 2020), as in the findings described here. These findings suggest that depression in women with endometriosis could be largely, but not entirely, a consequence of pain. In the data reported here, pelvic pain and depression were also positively related in women with PCOS and controls, but for these women, neither pain nor depression affected RMET scores. The positive effect of depression and pelvic pain on cognitive empathy in women with endometriosis only thus requires further explanation.

Subclinical levels of depression, and a past history of depression, have been linked with enhanced RMET performance among healthy women (Harkness et al., 2005, 2010), with these results attributed, in part, to higher psychological attention to social and emotional cues among women with mild depression. More generally, the capacity to decode the cognitive and emotional states of other people has phylogenetic and developmental roots in mechanisms that evolved for evaluating and responding to psychological and physical pain (Tucker, Luu, & Derryberry, 2005). These lines of research indicate possible routes through which both physical pain and depression could be linked to higher levels of empathy, especially under specific hormonal conditions, such as among women with endometriosis. For example, self-reported pain sensitivity has been positively associated with levels of emotional empathy, among healthy

individuals (Ren et al., 2020), and pain sensitivity is higher in women with endometriosis than in controls (Zheng et al., 2019).

A hormonal explanation may also be applicable to the finding that women with PCOS who were medicated with spironolactone exhibited significantly higher RMET scores compared to unmedicated women with PCOS, or women with PCOS taking other medications. As noted above, in contrast to endometriosis, PCOS typically involves increased serum testosterone levels, and apparent reductions in oxytocin activity. Spironolactone exerts antiandrogenic activity through its antagonism of the androgen receptor (Carone et al., 2016), and it can reduce serum testosterone (Lobo et al., 1985). Given that higher testosterone in women has been associated with lower RMET scores (Van Honk et al., 2011; Khorashad et al., 2018), the finding that anti-androgenic drugs are associated with better RMET performance is consistent with previous research. This hypothesis would benefit from experimental tests, especially given the frequent use of spironolactone, and other anti-androgenic agents, in women with PCOS and other conditions.

4.5.1. Limitations

This study is subject to several limitations. First, participants self-reported their diagnosis, and given the clinical challenges of diagnosing PCOS and endometriosis, some of these diagnoses could be incorrect. However, several questions were used to confirm such diagnoses, and specific, rigid criteria were used for assigning participants to the diagnostic group. Second, sample sizes were relatively small, especially for making comparisons between women taking and not taking different kinds of medication. There was also a significant difference in age such that control women were younger, which likely reflects the duration of time that it takes for women to receive diagnoses. Third, the women with PCOS who were medicated with spironolactone may have been subject to ascertainment bias, since these women may have had more severe PCOS or may have been more concerned about androgenic symptoms; these differences could independently affect RMET performance. Fourth, part of our recruitment strategy involved inviting women from PCOS, endometriosis, and pelvic pain support groups: women who choose to participate in support groups may not accurately represent the broader population of women with endometriosis or PCOS. Fifth, levels of hormones,

including oxytocin, as well as pelvic pain severity varies with menstrual cycle phase and we did not collect data or control for menstrual cycle phase. Finally, the study did not involve quantification of hormone levels for testosterone or oxytocin, which would have allowed more definitive tests of the hypotheses addressed.

4.5.2. Conclusions

Cognitive empathy is fundamental to human social cognition and the experience of positive and fulfilling social relationships. This study has described evidence that women with endometriosis and PCOS vary significantly in their cognitive empathic skills, in direct relation to central aspects of the hormonal and psychological symptoms, and some treatments, that characterize these two disorders. Additional studies are required to experimentally evaluate the apparent links of hormonal and psychological factors with cognitive empathy and the symptoms of endometriosis and PCOS.

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Chapter 5.

Niles Newton's triune goddess: Sex-birth-breastfeeding interactions shape women's capacity for pleasure

Natalie L. Dinsdale & Bernard J. Crespi

5.1. Abstract

Evolutionary explanations for women's sexual response largely focus on whether or not female orgasm serves a reproductive function. Comparatively underexplored are the proximate and evolutionary causes of women's capacity for extensive sexual pleasure through prolonged arousal, elaborate orgasm phenotypes, and intense emotional and psychological shifts. To explore this 'expanded sexual response' of women, we draw on the legacy of the late reproductive biologist, Niles Newton. Through her comparative research, Newton maintained that sex, birth, and lactation demonstrate numerous interrelationships due to their shared reliance on oxytocin. Newton characterized a set of similarities between sexual arousal and orgasm with natural, undisturbed labour and birth, but the role of these phenotypic interrelationships have yet to be integrated into evolutionary models of female sexual response. We extend Newton's work in four key ways: (1) contextualize female orgasm and pleasure more broadly as involving oxytocin-mediated 'immobility without fear'; (2) describe functional links between physical and psychological processes involved in both sex and birth; (3) forward a novel hypothesis whereby sexual activity provides 'practice for parturition'; and (4) examine cervical orgasm as involving activation of parturition mechanisms in a sexual context. We review and synthesize literature on oxytocinergic regulation of female reproduction, genito-pelvic reflexes in sex and birth, pelvic floor interventions, psychological correlates of sexual function, and birth psychology. Newton's emphasis on understanding the entire spectrum of female reproductive processes – sex, birth, and lactation – has practical implications for women's health and can fruitfully guide research into the diverse and elaborate nature of female sexual response.

5.2. Introduction

Women's sexual nature is a source of mystery that inspires investigation of, and debate over, its origins, functions, and diverse ranges of expression. During sexual activity, women are capable of experiencing prolonged periods of sexual arousal, multiple types of orgasms that vary in duration and intensity, and profound alterations to their sense of self and reality (Masters & Johnson, 1966; Darling, Davidson, & Jennings, 1991; Sayin, 2011; 2012; King & Belsky, 2012; Levin, 2015). This "inordinate sexuality" of women (Sherfey, 1972, p. 140) has been recognized and celebrated across time and culture (Korda, Goldstein, & Sommer, 2010), yet represents a relatively nascent topic in the biological and evolutionary sciences (Hrdy, 1997).

Here, we revive and extend a framework developed by the late reproductive biologist, Niles Newton, to explore the female capacity for deep and extensive sexual pleasure and orgasm. Newton maintained that both *sexual* processes (e.g. orgasm) and *reproductive* processes (e.g. lactation) must be included in a complete understanding of female sexuality, and that distinctions between the two are generally artificial as well as male-centric (Newton, 1955). During the course of Newton's career, sexual taboos were relaxing and research into female sexuality rapidly expanded. Newton, however, was critical of much of this research, including the pioneering work of Alfred Kinsey, as Kinsey's (1953) work examined only those aspects of female sexuality that could be directly compared to male sexuality. Assuming that the expression of a given trait or process in males represents the standard against which females should be compared is called androcentrism (Lloyd, 2005).

Research into the origins and functions of female orgasm is influenced and distorted by androcentric bias (Lloyd, 2005). Indeed, studies concerning the phenotypic structure of female sexuality more broadly generally assume that male-female conflicts over mate choice, conception, and resources must be the primary drivers in shaping female sexuality (e.g. Thornhill & Gangestad, 2015; Wheatley & Puts, 2015), which represents a more subtle example of androcentrism. Such bias occludes how female-specific evolutionary pressures and physiological mechanisms may shape women's capacity for sexual pleasure. Newton recognized female reproductive biology as a distinct phenomenon and explored the entire spectrum of women's reproductive

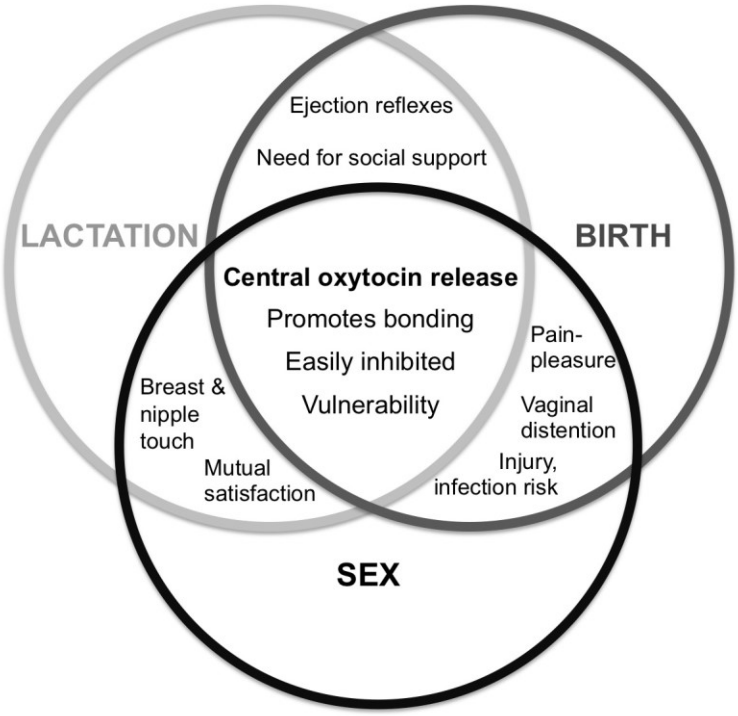
processes, from menstruation to orgasm to lactation. We use this female-centric framework as our guide to investigate how the female-specific process of parturition shapes women's sexual nature.

Bridging sexual and reproductive processes in the tradition of Niles Newton offers key insights into questions about female sexual response: are there different kinds of female orgasm, and if so, do these orgasms have specific functions? More importantly, this approach generates new and potentially more fruitful questions, such as: what are the proximate and evolutionary bases for expanded sexual response in women? How might a deeper understanding of the interrelationships between sex, birth, and lactation improve women's health and wellbeing?

5.3. Hypotheses

Niles Newton described female sexuality as more *diverse and elaborate* than male sexuality, because female reproduction is contingent upon participation in three reproductive partnerships, coitus, birth, and lactation, whereas male reproduction is contingent only upon coitus (Newton, 1955). Coitus, birth, and lactation are mediated by shared psychophysiological mechanisms, most notably the oxytocin system, which generates similarities among and spillover between the three partnerships in females (Figure 5.1). That functionally significant processes typically activated in one context (e.g. nipple erection during lactation) can be pleasurable and eroticized in a sexual context (human-specific breast sex; Levin, 2017) is what Newton means when she describes women as having a more *varied sexual heritage* than men (Newton, 1955; 1973/1992). Newton's ideas concerning the causes of elaborate female sexual response have yet to be meaningfully integrated into modern biological and evolutionary accounts of female sexuality. We seek to do so here.

Figure 5.1 Niles Newton's characterization of women's varied sexual heritage

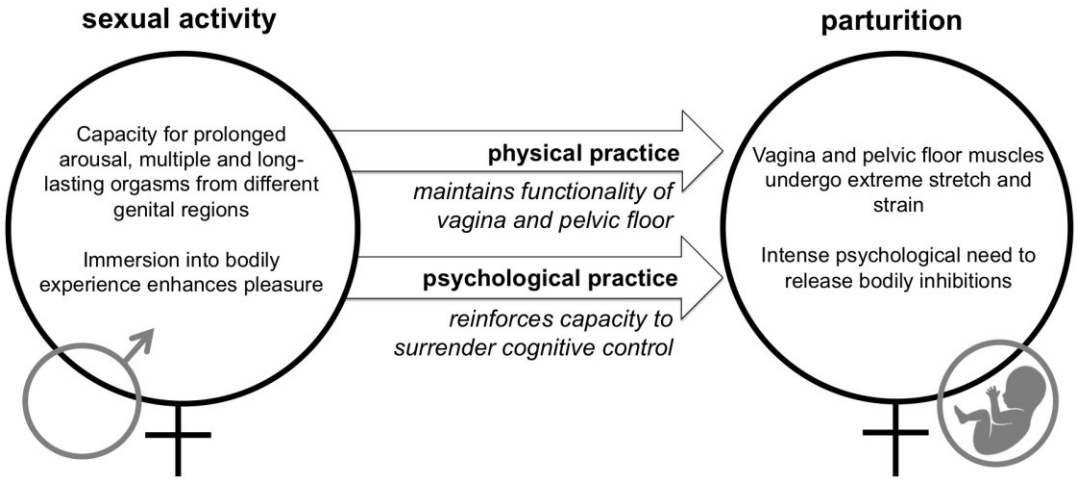


Niles Newton's characterization of women's varied sexual heritage, which emerges as a result of participation in three reproductive partnerships. The central release of oxytocin during sex, birth, and lactation underlies phenotypic similarities among and spillover between these partnerships in women.

First, we propose that the phenotypic structure of female sexual response, particularly the capacity for deep and extensive sexual pleasure through prolonged arousal, elaborate orgasms, and absorbed states of mind, involve secondary expression of labour and birth mechanisms in sexual contexts. These mechanisms may include oxytocin-mediated *immobility without fear,* genito-pelvic reflexes, and psychological states that support 'letting go'. Second, we suggest that activation of labour and birth mechanisms in a sexual context may provide benefits to women during later parturition (Figure 5.2). Such 'practice for parturition' is expected to occur via physical and psychological pathways, such that female sexual pleasure: (1) enhances awareness and maintains functionality of pelvic floor muscles and reflexes through regular and varied use; and (2) familiarizes women with the psychological experience of 'surrendering' into a bodily experience under which they have diminished control. Third, we explore cervical

orgasm as a specific capacity of female sexual response that involves activation of parturition mechanisms.

Figure 5.2 Overview of the 'practice for parturition' hypothesis



To investigate these three interconnected ideas, we first provide relevant background information, defining and describing the stages of desire, arousal, and orgasm. Second, we introduce Niles Newton's body of work concerning the roles of oxytocin in mediating sex-birth-lactation interrelationships. Third and fourth, we extend Newton's work by comprehensively reviewing the literature to describe in detail the physical and psychological functional links between sex and birth. Fifth, we review a small body of existing studies to examine the prediction that pre-parturition sexual function impacts labour and birth outcomes. Sixth, we examine labour and birth mechanisms that may contribute to the existence of cervical orgasm in women. Finally, we synthesize these numerous lines of inquiry to demonstrate the depth, utility, and generativity of Newton's framework for understanding female sexuality.

5.4. Sexual response

Investigating the interrelated functions of traits and processes first requires a clear understanding of the variables of interest, so here we describe a basic model of sexual response. Sexual response involves the stages of desire, arousal, orgasm, and a resolution or refractory period (Masters & Johnson, 1966; Kaplan, 1974). Each of these

phases demonstrates sex differences, and women do not reliably experience all of the phases, nor do they necessarily move through the phases in a sequential manner (Masters & Johnson, 1966; Baumeister, Catanese, & Vohs, 2001; Basson, 2001; Levin, 2003a), as described in detail below.

5.4.1. Desire

Sexual desire emerges when an individual attends to external, sensory data such as visual or tactile stimuli or olfactory cues that are contextualized as erotic, or when internal processes elicit erotic thoughts and feelings (Georgiadis & Kringelbach, 2012). These internal and external aspects of desire depend upon dopamine-mediated activity in the ventral striatum, nucleus accumbens, and amygdala, which serve the functions of recognizing sexual opportunity and motivating sexual behaviour (Georgiadis & Kringelbach, 2012). In addition to dopamine, the hormones oxytocin, norepinephrine, and melanocortin are also involved in stimulation of sexual desire through their activity in the limbic system and hypothalamus (Pfaus, 2009). Men tend to experience higher levels of sexual desire than women, and women experience higher rates of chronically low or absent sexual desire that interferes with their wellbeing, apparently reflecting maladaptive extremes of evolved sex differences (Peplau, 2003; Baumeister et al., 2001; Georgiadis & Kringelbach, 2012; Brotto, 2017).

5.4.2. Arousal

Sexual arousal encompasses physiological changes. Activation of the sympathetic and parasympathetic nervous systems increases oxygen pressure and promotes blood flow to the genitals, causing pelvic vaso-congestion and lubrication in females and penile erection in males (Georgiadis & Kringelbach, 2012). The increased blood flow created by sexual arousal in women nourishes the vagina, clitoris, labia, breasts, skin, and pelvic musculature (Levin, 1992; 2003b). Brain regions underlying sexual arousal include the hypothalamus, anterior cingulate cortex, putamen, and insula (Stoléru et al., 2012). Deactivation of the temporal lobe also predicts higher sexual arousal (Georgiadis et al., 2006). There is a bidirectional feedback relationship between desire and arousal such that perception of genital arousal can enhance desire and recognition of desire can enhance arousal (Bancroft, 2002).

Females experience sexual arousal in response to a greater range of erotic stimuli than do males, and males tend to demonstrate sexual arousal in response to stimuli consistent with their sexual orientation (Chivers et al., 2004). Such non-specific sexual arousal in women has been hypothesized as an adaptation that physically protects women in case of nonconsensual penetration, or a mechanism that promotes female-female bonding in polygynous marriages (Sawatsky et al., 2018; Kanazawa, 2017). Given the role of sexual arousal in maintaining the integrity and function of the female pelvic floor (Levin, 2003b), however, non-specific and prolonged female sexual arousal could more parsimoniously be framed as a mechanism for eliciting frequent sexual arousal across environmental and situational contexts. Compared to males, females are more likely to suffer from persistent genital arousal disorder (PGAD), a condition whereby unwanted and intrusive genital arousal occurs in the absence of sexual desire and fails to remit after orgasm (Jackowich et al., 2016). The female bias in PGAD cases affirms findings of sex differences in mechanisms contributing to the cessation of genital arousal (Levin, 2003a).

5.4.3. Orgasm

Orgasm constitutes the subjective peak of the sexual response cycle and is described and defined in a multitude of ways that illustrate the psychological and physiological significance of the event. Most broadly, orgasm involves a pleasurable release of sexual and psychic tension with co-occurring rhythmic, involuntary contractions of the genito-pelvis and body (Mah & Binik, 2001). Compared to males, females require more time to reach orgasm, experience orgasm less consistently during heterosexual coitus, and may experience more distinct kinds of orgasm dependent on the site of stimulation (Lloyd, 2005; Levin, 2015; King & Belsky, 2012).

Up to half of women have multiple orgasms and some women experience status orgasmus, orgasms that last for one minute or much longer (Masters & Johnson, 1966; Darling et al., 1991). Some women have multiple and long-lasting orgasms coinciding with profound perceptual, emotional, and spiritual experiences, a phenomenon long-recognized in myth and history (e.g. Greek tale of Tiresias), but only recently described and labeled as *expanded sexual response* (ESR) in a scientific context (Sayin, 2011; 2012; 2017). Here, we use the phrases expanded sexual response and extensive sexual

pleasure interchangeably. The capacity to have multiple orgasms in natural sexual settings may be specific to human females, as adult human males apparently require practice and training to do so, and data for such a feat in non-human animals is lacking (Levin, 2017).

Following orgasm with ejaculation, males experience a temporary refractory period where they are incapable of becoming physiologically aroused, but females can remain aroused or become increasingly aroused whether orgasm occurs or not (Levin, 2003a; Levin, 2009). Ejaculatory mechanisms thus inhibit sexual arousal in men, but specific mechanisms for the cessation of physiological sexual arousal in women have yet to be identified (Levin 2003a; Levin, 2009). A refractory period may occur following ejaculatory orgasms in women, but this remains unverified (Levin, 2009). To the best of our knowledge, the capacity of women to remain sexually aroused post-orgasm has yet to be considered as functionally significant. While the male orgasm provides a reliable method for transporting sperm, the function – if there is one – of the female orgasm remains unknown and is heavily debated (Lloyd, 2005; Levin, 2015).

Types of orgasm

One persisting question in the field of female orgasm research, which is closely tied to the 'function of female orgasm' question, is whether or not women have different types of orgasm. There are anatomical, neurological, and qualitative approaches to this question, and its answer informs evolutionary accounts of female orgasm, as different types of orgasm could potentially represent distinct functions and effects from evolutionary legacies.

Women report more distinct kinds of orgasm dependent on the site of stimulation (Lloyd, 2005; Levin, 2015; King & Belsky, 2012; Jannini et al., 2012). When rhythmically stimulated, body parts with high concentrations of sensory receptors are generally capable of producing orgasm, including non-genital regions (Komisaruk & Whipple, 2011). Stimulation of diverse genital and bodily sites can elicit orgasm in women with women reporting orgasms from stimulation of the clitoris, periurethral glans, urethral meatus, labia, vagina, cervix, g-spot, nipples, mouth, anus, or combinations of the above sites (King & Belsky, 2012; Levin, 2014; Levin, 2015; Sayin, 2017). That orgasm can occur from stimulation all over the body, and from thought alone, indicates that the

capacity to mount and pleasurably release tension is a more general function of the central nervous system, which is particularly well developed in the genital region (Komisaruk & Rodriguez del Cerro, 2021).

Orgasm from direct clitoral stimulation is most commonly described by women, while orgasm from vaginal, penetrative stimulation occurs less frequently (reviewed in Lloyd, 2005). For example, Cutler and colleagues (2000) found that in a sample of 132 healthy women, 98% reported that the clitoris played a major role in generating orgasm, while 86% identified the vagina as important, and 46% reported the cervix as playing an orgasmic role. Bronselaer, Callens, De Sutter, and colleagues (2013) sampled 749 women and found that 94% could orgasm from clitoral stimulation and 70% from deep vaginal stimulation. In a recent study, Herbenick, Fu, Arter and colleagues (2018) found that 37% of women surveyed required clitoral stimulation to orgasm and 18% could orgasm from penetration during intercourse.

One anatomical perspective holds that all female orgasms originate from the clitoris, which is the homologous organ to the penis in males (Puppo & Puppo, 2015). These authors argue that when women experience an orgasm that feels as though it has originated from vaginal stimulation (via penetration or intercourse), the orgasm is actually a consequence of non-vaginal, surrounding erectile organs, which include the clitoris, vesibular bulbs, labia minora, and corpus spongeiosum of the female urethra; collectively referred to as the ‘female penis’ (Puppo & Puppo, 2015). Under this perspective, so-called ‘vaginal’ or ‘cervical’ orgasms do not exist.

There is evidence, however, that clitoral compared to vaginal stimulation produces different patterns of smooth and striated muscular contractions in the genito-pelvis (Levin, 2001). Stimulation of the clitoris, vagina, and cervix each map onto distinct but overlapping regions of the sensory cortex (Jannini, Rubio-Casillas, Whipple, et al., 2012). Innervation of these genital sites involves multiple nerve pathways, which both overlap and diverge between the sites (Pfaus et al., 2016). These findings together indicate that stimulation of different genital regions may produce a variety of subjective experiences for women.

Self-report data are limited in their ability to answer the ‘types of orgasm’ question, as the intensity of sexual arousal and orgasm makes it difficult for women to

clearly identify which anatomical site has generated the orgasm (ambiguity problem; Levin 2011, 2012, 2015; Prause, 2012). Further, direct and indirect stimulation of multiple genital sites may synergistically provide sufficient activity to cross the orgasmic threshold (Safron, 2016); trying to localize an orgasm to one genital site may be futile.

It is also difficult to compare orgasm types across studies, as terminology and precision of research question vary greatly (Lloyd, 2005). For example, a 'coital' orgasm could occur during intercourse with a partner of either sex, with or without concomitant indirect or direct clitoral stimulation. A 'vaginal' orgasm could occur during coitus and thus be the same a coital orgasm, or it could occur from non-coital forms of sexual stimulation involving penetration of the vagina.

Deep and surface orgasms

With these limitations in mind, women's qualitative descriptions of orgasm do reflect two broad types of orgasm – 'deep' and 'surface' (King et al., 2010; King & Belsky, 2012; McCormick, Todd, Schmuldt et al., 2019). So-called 'surface' orgasms feel as though they are generated by the external genitalia and have the nature of being relaxing. 'Deep' orgasms feel as though they emerge from within the body and involve full-body sensations and psychological shifts such as loss of self and a sense of floating (King & Belsky, 2012).

These 'deep' orgasms are reported to occur more frequently in partnered as well as penetrative sexual contexts (King & Belsky, 2012). Factors that add to the intensity of these 'deep' orgasms thus likely involve connection and communication with the sexual partner as well as stimulation of internal genitalia. Indeed, women are more likely to orgasm during coitus when they assume a face-to-face position with their partner (Krejčová, Kuba, Flegr, et al., 2020). Gazing into someone's eyes, or receiving the gaze of another is known to increase oxytocin levels (Carter, 2017). Women describe orgasms occurring during sexual intercourse (coital orgasms) as involving 'whole body' pleasure (Palmer, 2014). Female orgasm, and 'deep' orgasm in particular, appear to involve, to some researchers, features consistent with a reproductive function.

Cervical orgasm

Belonging to the category of 'deep' orgasms are orgasms elicited from cervical stimulation. A recent review of female sexuality that drew on the expertise of researchers as well as therapeutic practitioners summarized cervical orgasms as follows:

> When, however, a cervical orgasm does occur, a broad spectrum of profound experience is reported: a calming, grounding effect on the female psyche is possible, as well as heightened states of consciousness and transcendental states with temporary immobilization, visions and sensations of physical dissolution and merging into oneness with everything. (Nemati & Weitkamp, 2020, p. 13).

Earlier medical and sexual perspectives described the cervix as an anatomical site with few sensory nerves and poor sensitivity (to the extent that local surgeries are still commonly performed on women's cervixes without anesthetic) (Kinsey, 1953). However, an extensive body of work (Komisaruk & Wallman, 1973; Komisaruk & Wallman, 1977; Komisaruk & Whipple, 1984; Whipple & Komisaruk, 1988; Komisaruk & Sansone, 2003; Komisaruk et al., 2004) has reported evidence for a pain-blocking effect produced by cervical stimulation. First, as discovered in rats and later confirmed in women, this analgesic effect occurs via mechanical stimulation of the cervix and upper vagina, and is mediated by multiple neurochemical systems, including noradrenergic, serotoninergic, and opioid pathways (Komisaruk & Sansone, 2003). Importantly, in women, the more pleasurable the stimulation, the stronger the pain-blocking effect, and the pain blocking specifically impacts pain and not overall tactile sensitivity (Whipple & Komisaruk, 1988). These studies also revealed that the vagus nerve – which transmits sensory information from the viscera to the brain without entering the spinal cord - innervates the cervix and carries sensory information to the brain. Komisaruk and colleagues suggest that the analgesic effects of vaginocervical stimulation plays a role in both coitus and parturition, which is explored below.

Further evidence for a pleasurable role of cervical stimulation comes from women's experiences following hysterectomies. When women get their uteri surgically removed, due to painful disease, they may have their uterus and cervix removed, or the cervix may be left intact. Some clinicians recommend that women's sexual history be examined before a decision regarding form of hysterectomy is made, as women who

report cervical orgasms may experience a reduction in sexual pleasure and orgasmic capacity following surgery (Parikh & Lesseps, 2000).

The role of cervical stimulation in eliciting special modes of female-only pleasure is also described in approaches to sexuality from different cultures, most notably Tantra. Tantra refers to a diverse body of beliefs and practices with Asian roots that seeks to creatively access the divine energy of the universe in an effort to liberate the self (White, 2000). According to sexual teachings of some forms of Tantra, the vulva, vagina, and cervix represent three gateways into female pleasure that must be gradually and sequentially opened through careful attention, time, and stimulation (personal communication, C. Lemieux, May, 2021). Thus, cervical stimulation should not be attempted unless a woman is in a very high state of relaxation and sexual arousal. In Tantric practice, the cervix is perceived as having connections with the heart, so its stimulation can result in powerful emotional cleansing (Nemati & Weitkamp, 2020). Connections between the heart, cervix, and emotions, as noted by ancient and modern practitioners of Tantra, fit with what is known concerning human physiology: the vagus nerve innervates the gut and cervix and is responsible for parasympathetic regulation of the heart. Stimulation of the cervix thus releases large quantities of oxytocin into the central nervous system, which has diverse effects on the body, including a wide range of cardio-protective and stress-reducing benefits via the action of oxytocin receptors in all chambers of the heart (Jankowski, Broderick, & Gutkowska, 2020).

Proposed functions of female orgasm

Of the sexual phases described above, much of evolutionary research into female sexuality has focused on desire and orgasm, especially the function of cyclical shifts in desire and the frequency, correlates, and possible functions of orgasm in women (Roney & Simmons, 2013; Motta-Mena & Puts, 2016; Thornhill & Gangestad, 2015; Wheatley & Puts, 2015; Puts et al., 2012a; Lloyd, 2005; Baker & Bellis, 1993). Comparatively underexplored is the evolutionary history and significance of highly-expressed and varied orgasm phenotypes, prolonged and non-specific sexual arousal, and the apparent lack of refractory period in women (Levin, 2003a; 2009); this set of phenotypes comprise women’s capacity for extensive sexual pleasure and its absence from research might be attributed to androcentric bias, as such capacities are not

commonly observed in males. Here, we briefly review adaptive and non-adaptive explanations for female orgasm and then discuss limitations to these explanations.

The mate choice hypothesis positions female orgasm as an adaptive mechanism for influencing paternity; it is based on the contested notion that oxytocin-induced orgasmic contractions draw sperm into the uterus and increase the likelihood of conception (Baker & Bellis, 1993; Puts et al., 2012b; Ellsworth & Bailey, 2013; Wheatley & Puts, 2015; Levin, 2017). Consistent with the mate choice hypothesis, female coital orgasm frequency does increase when male partners demonstrate presumably fitness-enhancing traits such as humour, warmth, attractive body scent, physical attractiveness, creativity, dominance, and masculinity (King & Belsky, 2012; Puts et al., 2012b; Sherlock et al., 2016) Further, women in King and Belsky's (2012) study described 'deep' orgasms as involving 'sucking' sensations, which the authors interpret as support for an orgasm-induced sperm transport mechanism.

The mate choice account faces two key reservations. First, the only reported correlation between female orgasm and fertility disappears after controlling for relationship duration, suggesting that increased sexual contact jointly explains conception probability and orgasm frequency (Zietsch & Santilla, 2013). Second, the proposed role of orgasm-released central oxytocin in enhancing sperm transport through the female reproductive tract is not well supported by evidence (Levin, 2017). Sperm transport occurs rapidly from the cervix to the fallopian tube ipsilateral to the ovary containing the ovulating follicle even in the absence of sexual arousal. Transport occurs cyclically throughout the estrous cycle, via uterine-produced oxytocin and its synergy with estrogen; additional central oxytocin is not required for this process to occur (Kunz et al., 2007). Also, sperm transport that occurs too rapidly could cause uptake of sperm prior to decapacitation, decreasing the likelihood of fertilization (Levin, 2017). Furthermore, given that sexual arousal involves a steady increase in central oxytocin release preceding orgasm (Carmichael, Humbert, Dixen et al., 1987), it is unclear why orgasm would be necessary to activate the supposed upsuck functions of oxytocin. While vulvar and clitoral stimulation and corresponding sexual arousal create numerous changes in the female reproductive tract that promote conception (Levin, 2020), evidence for a specific role of 'deep' orgasm in increasing likelihood of conception through oxytocin-mediated sperm transport remains unsubstantiated.

Pair-bond hypotheses for female orgasm propose that the rewarding but difficult-to-induce nature of female orgasm reinforces copulation with males who are highly investing (Fleischman, 2016). For example, relationship factors such as intimacy, passion, love, and satisfaction predict female coital orgasm frequency (Costa & Brody, 2007). Because variable reinforcement is powerful in shaping behaviour, the elusive nature of the female orgasm may be useful in conditioning women to stay with men who intermittently apply the necessary effort to assist their female partners in reaching orgasm (Fleischman, 2016). Both the mate choice and pair-bond hypotheses for female orgasm have empirical support in terms of predicting orgasm frequency (Wheatley & Puts, 2015), but these accounts do not clearly and adequately address the physiological capacity of females to experience extensive sexual pleasure via prolonged arousal and multiple and long-lasting orgasms.

In Lloyd's (2005) extensive review of evolutionary research on female orgasm, she characterizes Niles Newton as a proponent of the pair-bond hypothesis for female orgasm. Though Newton (1973/1992) did state that sexual pleasure and orgasm promotes relationship harmony between a woman and man, she does not claim that orgasm exists *because* of, or *for,* this pair-bonding function. Newton suggests sexual pleasure (not orgasm exclusively) to be a biological building block for intimate family life. Specifically, Newton describes females as engaging in care-taking behaviour of males, such as cooking and emotional caring, following coital pleasure.

Curiously, in her review of Newton's ideas, Lloyd (2005) misgenders Newton as male (p. 62), and then claims that Newton links the existence of female orgasm with a feminine gender role, presumably because of Newton's emphasis on female care-taking behaviour. We disagree with Lloyd's position on Newton's work for two reasons. Firstly, Newton does not make narrow claims about the existence or function of female orgasm: she describes a link between sexual pleasure, which may include orgasm, and care-taking behaviour. Secondly, Newton's (1973/1992) characterization of the role for pleasure in relationship building cannot be separated from her work on oxytocin-mediated interrelationships between sex, birth, and lactation. All three of these reproductive partnerships involve pleasure and care-taking behaviour (Figure 1). The psychophysiological mechanisms that contribute to sexual pleasure and care-taking in coitus overlap with the mechanisms that motivate satisfaction with and care of a

vulnerable infant: these linkages are central to female reproductive success. Lloyd's (2005) choice to focus solely on orgasm gives an incomplete account of Newton's analysis of interlinked female reproductive responses.

Contrasting with the mate choice and pair-bond accounts for female orgasm is the by-product account, which holds that women exhibit orgasm as a consequence of strong selection on the male ejaculatory reflex and shared embryological development (Symons, 1979; Lloyd, 2005). Low rates of female orgasm during coitus as well as high variability in female orgasmic response are broadly consistent with the by-product account, because presumably, if orgasm serves a key reproductive function such as transport of sperm from desirable mates, then it should occur more reliably during heterosexual intercourse (Lloyd, 2005). Within the byproduct framework, the female capacity for multiple orgasms is conceptualized as an underdeveloped expression of the orgasm phenotype, as prepubescent boys can have multiple orgasms before ejaculation develops (Lloyd, 2005). However other researchers maintain that aspects of female orgasm are better considered as elabourations of the orgasm phenotype, since multiple orgasms and status orgasmus involve multiple neural pathways and bodily regions and, overall, involve a greater expenditure of time and energy relative to single orgasms (Sayin, 2011; Wheatley & Puts, 2015).

A second non-adaptive account hypothesizes that orgasm in women is a vestigial response remaining from evolutionarily-ancient modes of ovulation (Pavličev & Wagner, 2016). Induced ovulation, where a female's egg is released through neuroendocrine reflexes elicited by sexual activity, evolved prior to cyclical ovulation. This hypothesis thus proposes that as cyclical ovulation emerged, orgasm and ovulation were decoupled, and a vestigial orgasm reflex was retained in women (Pavličev & Wagner, 2016). While this hypothesis may explain the origin of the orgasm reflex in women, it does not purport to explain how orgasm in women may have further evolved to fulfill other reproductive or mating functions (Wagner & Pavličev, 2017).

These evolutionary accounts of women's sexual nature remain limited for three key reasons. First, most research focuses on female orgasm, but orgasm is only one aspect of sexual behaviour and physiology, and examining it in isolation from the other aspects and phases results in an incomplete view of the possible functions of female sexual phenotypes. Second, both adaptive and non-adaptive accounts of female orgasm

exclude a suite of psychological and physiological phenotypes that contribute to, and coincide with, orgasm in women. Features of female orgasm, and female sexuality more broadly, that are salient to an evolutionary account, such as sex-specific psychological elicitors of desire and arousal, increased pain tolerance, and the capacity for different kinds of long-lasting and multiple orgasms have yet to be integrated into an evolutionary framework (Swartz, 1994; Sayin, 2012; Levin 2015). Third, aspects of female sexuality that most clearly differ from male sexuality, such as prolonged arousal, lack of refractory period, and multiple orgasms generated from numerous genital and bodily sites, have yet to be considered as significant. That female-specific and female-elaborated sexual phenotypes have yet to meaningfully enter evolutionary studies of women's sexuality exemplifies what Newton described as 'male-centric': because these features are not commonly observed in male sexuality, they do not receive in-depth research attention.

To further understand the female capacity for extensive sexual pleasure, multiple phases of sexual response in women need to be examined as a coherent set of features, including co-occurring psychological and physiological phenotypes, and especially those characteristics of female sexuality that appear to involve sex-specific elabouration (Wheatley & Puts, 2015). Also, the vagina, cervix, and uterus are developmentally and functionally integrated, multi-purpose organs, involved in coitus, sperm-handling, menstruation, conception, childbirth, and placental expulsion. Research into female orgasm, and sexual response more broadly, would benefit from acknowledging that psychological and physical effects of female nipple and genito-pelvis stimulation represent both sexual ('recreative') and reproductive ('procreative') functions (Levin, 2002); such a perspective is female-centric.

5.5. Introducing Niles Newton's work

Niles Newton (1923-1993) was a prolific scientist and popular writer as well as a wife and mother of four children (Martucci, 2018). She studied and wrote about female reproductive biology as well as women's wellbeing, applying both comparative and qualitative approaches to investigate interrelationships between lactation, birth, emotions, sexuality, and relationships. For example, she conducted a series of experiments that demonstrated how fear interferes with mammalian female reproduction through reducing oxytocin release, causally slowing labour progress and inhibiting milk

let-down (Newton, Foshee, & Newton, 1966; Newton, Peeler, & Newton, 1968). Newton's (1955) qualitative work with women emphasized how sociocultural factors impact birth and sexual expression: if shame is felt in one area (e.g. menstruation), it will likely have inhibitory effects on other processes (e.g. orgasm). In addition to laying a foundation for the resurgence of natural birth and 'back-to-breast' movements of the 1970s (Martucci, 2018), Newton's body of work also initiated a wealth of research into how the oxytocin system mediates mammalian intimacy (e.g. Carter & Getz, 1993; White-Traut, et al., 2009; Odent, 2009a, 2009b).

5.5.1. Oxytocin, immobility, and female reproduction

Niles Newton's perspective on female sexuality emphasizes the roles of the oxytocin system in jointly regulating sexual response, birth, and lactation. Female orgasm, and sexual pleasure more broadly, are thus framed as capacities of an oxytocin-mediated nervous system that promotes and pleasurably rewards close engagement in vulnerable, partnered, and selectively-relevant reproductive contexts. For example, in work directly influenced by Newton, Odent (2009b) describes oxytocin-mediated reflexes as weaving throughout orgasm, birth, and lactation: all of these can involve pleasurable release of tension coinciding with powerful emotions.

Oxytocin, a peptide hormone that emerged in conjunction with placentation, viviparity, lactation, and extended maternal care, is well known for its role in mediating social relationships (Crespi, 2015; Feldman, 2016). Particularly in females, oxytocin-mediated neural circuitry underpinning mother-infant bonding was co-opted to support romantic pair-bonding (Numan & Young, 2016; Crespi, 2015). Although the modulation of relating is perhaps oxytocin's most widely characterized function – alongside its crucial role in milk ejection and supportive role in parturition - oxytocin also exerts diverse anti-stress effects through its regulation of the autonomic nervous system. Parasympathetic effects linked to oxytocin release include promotion of immune functioning and bodily repair (Gouin et al., 2010; Elabd et al., 2014), cardiovascular regulation (Gutkowska et al., 2014), and energy homeostasis (Smith et al., 2015). These multiple effects are exerted through oxytocin's central release from the paraventricular nucleus (PVN) of the hypothalamus and subsequent entrance into general circulation, as

well as through its peripheral production in and action upon multiple tissues including the heart, ovaries, and uterus (Carter, 2014).

Central release of oxytocin during sex, birth, and nursing can be understood as enabling *immobility without fear* (Porges, 1998; Carter, 2014). Each of these reproductive acts requires relative bodily immobility, leaving involved participants vulnerable to external threat; in mammals, the capacity of the nervous system to adaptively immobilize ('play dead') in a threatening situation elaborated to serve the evolution of reproduction and bonding (Porges, 2007). The release of oxytocin in females during the close social engagement required of coitus, birth, and nursing permits a relaxation or deactivation of fight or flight responses that would normally be activated in vulnerable situations. Vulnerable situations elicit oxytocin release, which promotes positive emotional states and behavioural approach, regulating anxiety and increasing the ability to draw on relationships for stress reduction (Carter, 2014; Feldman et al. 2016).

Mammalian female reproduction thus requires immobilization but without the accompanying defensive states. The periaqueductal grey matter located in the brainstem, rich in oxytocin receptors, regulates several bodily aspects of female reproduction, including lordosis (immobile posture for female sexual receptivity shared by many mammals) and kyphosis (immobile posture for nursing litters in animals such as rats) (Porges, 2007). By contrast, much of male sexual activity, such as erection, thrusting, and ejaculation involves motor loops that are regulated by periaqueductal regions distinct from those regulating immobilization. Oxytocin-mediated immobility thus plays a comparably much greater role in female reproduction, so oxytocin release during sexual arousal and orgasm in women should be considered in this broader context.

Whether or not oxytocin causally increases sexual arousal or is a by-product of it has yet to be fully elucidated, but its effects - in conjunction with dopamine - clearly compose part of the sexual-excitatory pathway in women (Borrow & Cameron, 2012; Veening et al., 2015; Pfaus, 2009). Importantly, oxytocin interacts with dopamine and endogenous opioids, two classical reward system modulators, shaping reward sensitivity, pleasure, and attachment (Esch & Stefano, 2005; Loth & Donaldson, 2021). Furthermore, psychological traits that can be understood as bridges between 'self' and 'other', such as extraversion, spirituality, and empathy all involve the oxytocin system

(Zhao et al., 2016; Andari et al., 2014; Holbrook et al., 2015; Wu et al., 2012). Re-contextualizing oxytocin release during female sexual pleasure in the framework of immobility without fear may help to illuminate causes of expanded sexual response in women, including the physiological capacity for extended arousal and elaborate orgasms, and the psychological capacity for altered modes of thinking and feeling.

5.5.2. Sex-birth interrelationships

One of Newton's key contributions was describing interrelationships among the reproductive partnerships of coitus, birth, and breastfeeding, as introduced and depicted above (Figure 5.1; Newton 1955, 1973/1992). She characterized these three partnerships as highly sensitive to environmental context, stimulatory of care-taking behaviour, and involving large quantities of central oxytocin release. As part of this work, Newton described a set of bodily, emotional, and sensory similarities of sexual arousal and orgasm with natural, undisturbed labour and birth, proposing that these sex-birth overlaps reflect shared psychophysiological mechanisms (Table 5.1; Newton, 1973/1992). Despite these insights, functional links between female sexual phenotypes and parturition have yet to be investigated as relevant to contemporary evolutionary explanations of female sexual response, even though diverse sources apart from Newton have also identified sex-birth interrelationships.

Psychoanalyst Helene Deutsch (1884-1982), for example, described the phenomenological similarities between coitus and birth, maintaining that parturition is imbued with the pleasure mechanisms of sex (Deutsch, 1944); she even suggested that birth represents the acme of sexual pleasure for women. Sex and birth educators have documented the ability of women to experience intense pleasure and passion during childbirth in doctoral research (Harel, 2007) as well as in film (*Orgasmic Birth;* Pascali-Bonaro, 2008). Several childbirth experts - including nurses, midwives, and obstetricians - maintain that freedom of sexual or 'primal' expression in a birth environment can positively impact mothers and their infants (Gaskin, 2003; Buckley 2004; Hotelling, 2009; Odent, 2009b; Mayberry & Daniel, 2016; but see Vissing 2015). We propose that a deeper understanding of the connections between sexuality and parturition, and sexuality and lactation, will illuminate biological and evolutionary causes of expanded sexual response in women.

Table 5.1 Phenotypic similarities between sexual arousal and orgasm with un-drugged, undisturbed childbirth (adapted from Niles Newton, 1973/1992)

Characteristic	Sexual arousal & orgasm	Undisturbed parturition
Breathing	Breathing quickens and deepens during arousal	Deep breaths during 1st stage of labour
	Interrupted breathing as orgasm approaches	Deep breaths with breath holding during 2nd stage of labour
Facial expressions	Facial expression indicating strain	Facial expression during 2nd stage of labour indicates great strain
Uterine activity	Rhythmic uterine contractions	Rhythmic contractions of uterus that intensify as labour progresses
Cervical activity	Cervical secretions may occur	Cervical mucus plug loosening is one sign of labour onset
Abdominal activity	Periodical contractions	Periodical contractions and urge to bear down during 2nd stage of labour
Bodily activity	Strength and flexibility evident during coitus	Unusual strength and body expansion required to birth baby
Psychological and emotional responses	Inhibitions are often released during intercourse	Uninhibited during parturition, especially as baby descends
	Wellbeing follows orgasm	Joy and ecstasy follows baby's emergence
Sensory perception	Whole body when sexually aroused becomes less sensitive to pain	Vulva becomes insensitive to sensation such that woman may be unaware of crowning
	Reduced sensory perception as orgasm approaches	Reduced environmental awareness as birth approaches

5.6. Extending Niles Newton's work

We focus on sex-birth interrelationships below, extending Niles Newton's work by describing functional linkages between physical and psychological aspects of coitus and parturition. While Newton listed bodily and emotional similarities between sexual arousal/orgasm and birth (Table 5.1), and explored the role of the oxytocin system in mediating these similarities, we provide a review of how the physical and psychological processes of sexual response overlap with, and *potentially influence*, later parturition. Newton acknowledged that inhibition of one reproductive process could interfere with another; we draw on existing literature to provide a deeper mechanistic understanding of such sex-birth interactions.

We frame our review through what we call the ‘practice for parturition’ hypothesis, which proposes that regular and varied sexual activity provides opportunity for women’s bodies and minds to prepare for the unfamiliar and challenging demands of childbirth. Under the ‘practice for parturition’ hypothesis, sexual activity prepares women for future labour and birth through: (1) enhancing awareness and maintaining functionality of pelvic floor muscles and reflexes through regular and varied use; and (2) familiarizing women with the psychological experience of ‘surrendering’ into a bodily experience. As a hypothesis with specific predictions for how sexual function can impact birth, ‘practice for parturition’ suggests that female-specific evolutionary pressures may play a key role in shaping female sexual phenotypes.

5.6.1. Physical links between sex and parturition

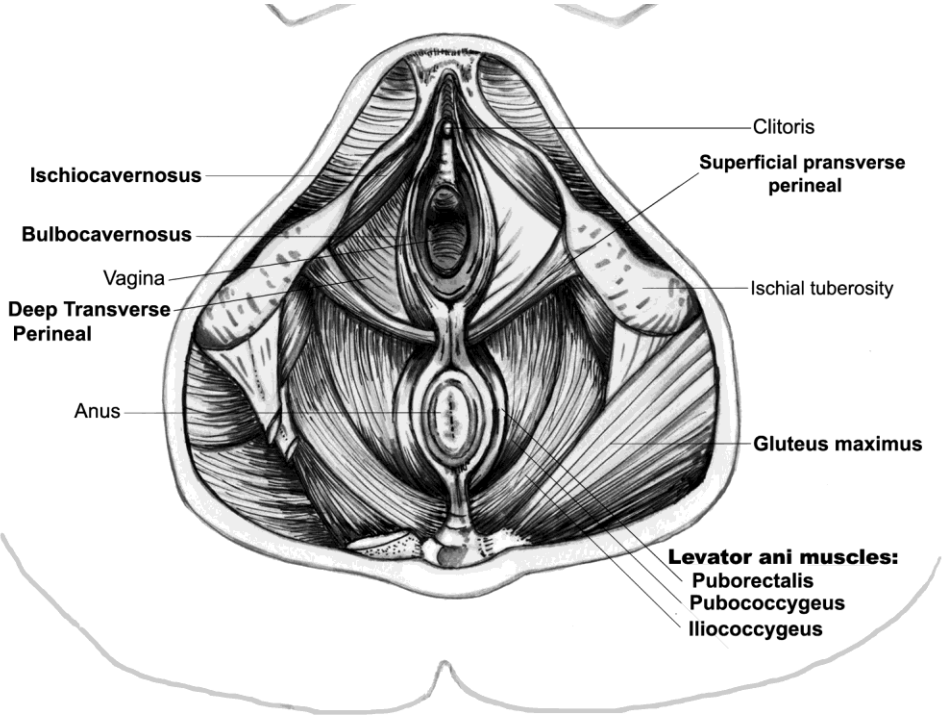
Sexual activity and parturition engage the same genital and pelvic structures (Levin, 2003b), which are under the control of several brain and brainstem regions, including the frontal cortex, sensory-motor cortex, cerebellum, basal ganglia, spinal cord, brainstem, and the periaqueductal gray matter (Blok et al., 1997; Zhang et al., 2005; Seseke et al., 2006). Due to connections between the pelvic floor and the limbic system, activity of the genito-pelvis is highly sensitive to emotional states and stimuli, especially stimuli evoking sexual desire, fear, or anxiety (Both et al., 2012; Broens et al., 2014; van der Velde et al., 2001).

The majority of research investigating relationships between sex and birth from physical or functional anatomical perspectives focus on how labour and birth affect postpartum female sexuality (e.g. Baytur et al., 2005; Dean et al., 2008; Leeman & Rogers, 2012; Andreucci et al., 2015). Here, we investigate the comparatively under-studied reverse: how might sexual stimulation of female genitalia and pelvic anatomy impact the ability of a woman’s body to cope with the physical demands of later labour and birth?

To explore this question, we used a comprehensive literature search strategy, deploying relevant key words and key word combinations including “genito-pelvic reflex”; “fetal ejection reflex”; “pelvic floor” and “parturition”. We also searched within articles citing the widely-used Female Sexual Function Index (FSFI; Rosen et al., 2000) for articles using the following keywords: “pelvic floor”; “parturition”; “labour”; and “birth”.

First we describe how reflexes of the female genito-pelvis (Figure 5.3) function in sex and parturition contexts, highlighting the dearth of knowledge in this area and briefly speculating on how known vaginal reflexes activated during sex could function in a parturition context. Second, we describe how the vagina and pelvic floor change to accommodate the stresses of labour and birth, including a brief overview of common pelvic floor injuries. Third, we review evidence assessing the impact of pelvic floor condition on sexual functioning and parturition outcomes. Finally, we review recent studies showing how specific interventions involving vaginal and perineal stimulation increase sexual pleasure and reduce birth injury.

Figure 5.3 Genital structures and muscles (bold) of the female pelvic floor



Stimulation of genital structures such as the clitoris or vagina generates automatic contractions (reflexes) in several pelvic floor muscles, causing the vaginal canal to change shape and size. Some pelvic floor muscles can be engaged voluntarily.

Genito-pelvic reflexes in sex

A reflex is a fast, involuntary movement caused by a stimulus. A genito-pelvic reflex occurs when stimulation or pressure of a genital or pelvic region elicits automatic contractions in another genital or pelvic region (Levin, 2002; Normandin & Murphy, 2011). Sexual stimulation elicits automatic reflex activity throughout the genitals and

pelvic floor; females have at least six genito-pelvic reflexes in comparison to one in males (Levin, 2003b; Levin 2007). In women, genito-pelvic reflexes appear to play important roles in coitus and conception, but their functions are not fully understood, due to their complexity, methodological challenges, and relatively little research attention (Spoelstra et al., 2018).

So far, research on female genito-pelvic reflexes has focused on how these reflexes contribute to women's sexual and conceptive functions, including sexual dysfunction (e.g. Ringrose, 1966; Levin, 2003b; 2007; Shafik, 2000). Given the dual-purpose nature of the vagina, it is logical to consider if and how these reflexes function during labour and birth. Birth-related reflexes have received some research attention, but mostly in animals (for ethical and methodological reasons) and largely in separation from the female sexuality literature.

To identify and examine genito-pelvic reflexes in experimental settings, researchers dilate the vagina with a balloon or other instrument to mimic the effects of penetration (Shafik et al., 2005; Shafik et al., 2007). The vagino-levator reflex widens the vaginal introitus and causes elongation and ballooning of the upper vagina during sexual arousal, creating a pocket of empty space in the upper vagina where the numerous components of semen mix before sperm transport occurs (Shafik, 1995; Shafik, 2000; Levin, 2003b; Broens et al. 2014).

The pelvic reflex occurs when cervical and vaginal stimulation elicits contractions of the bulbocavernosus and adductor thigh muscles, resulting in vaginal constriction (Levin, 2003b). Two high-pressure zones in the vagina function like sphincters, one near the introitus and another deeper in the vaginal canal (Broens et al., 2014). Even a very low distention of the vagina creates powerful contractions in these superficial and deep areas, referred to as the vagino-bulbocavernosus and the vagino-puborectalis reflexes, respectively (Shafik, 1993; 1995).

The vagino-bulbocavernosus reflex engorges the clitoris, contracts the vaginal introitus while the vagino-puborectalis reflex tightens the upper region of the vaginal canal. When these two sphincters are reflexively activated through vaginal distention, the strength and maximum duration of their contractions exceeds the strength and duration achieved during voluntary contractions (Broens et al., 2014). Together, the

pelvic reflex, the vagino-bulbocavernosus reflex, and the vagino-puborectalis reflex alter vaginal shape, and are thus presumed to be important for enhancing sexual pleasure for both parties during intercourse (Broens et al., 2014).

Stimulation of genital structures other than the vagina, including the clitoris, can elicit contractions in both the vagina and pelvic floor (Shafik et al., 2008; Levin, 2020). A variety of sexual activity, such as penile thrusting, digital penetration, or clitoral stimulation, are presumed to be capable of eliciting these genito-pelvic reflexes.

Genito-pelvic reflexes in birth

During labour and childbirth, the vaginal canal and pelvic musculature experience an extreme degree of stretch and pressure unparalleled by any other body part; how the vagina and pelvic floor withstand these extreme biomechanical demands is a relatively new research area (Ashton-Miller & DeLancey, 2009; Rostaminia et al., 2016). The pregnant female body's ability to accommodate parturition is partially supported by biochemically- and hormonally-mediated increases in the viscoelasticity of birth canal tissue (Tracy et al., 2018).

The most well-studied birth reflex is the Ferguson reflex. This reflex is initiated when the fetus descends upon the cervix, eliciting oxytocin release via the action of sensory neurons that respond to mechanical stretch of the cervix. As oxytocin levels increase, uterine contractility intensifies, which further increases the pressure of the fetal head upon the cervix, thus continuing the cycle via positive feedback (Ferguson, 1941).

Ferguson identified three additional patterns of reflex activity induced by vaginal dilation, in anesthetized rabbits. The rabbits showed biphasic uterine contractions that occurred independently of oxytocin, since destruction of the pituitary did not halt this specific pattern of uterine activity. Vaginal dilation also caused reflex activity of the abdominal muscles, related to the 'bearing-down' reaction of birthing. The fourth reflex identified by Ferguson involved a powerful contraction of the cervical region that travelled downward through the vagina via a peristaltic, expulsive wave (Newton, 1987; Ferguson, 1941).

Both Newton (1987) and Odent (1987; 2009a) characterized a fetus ejection reflex, but the two researchers used the term to describe different aspects of parturition.

The ‘Newton’ fetus ejection reflex is the same as the Ferguson reflex, but Newton’s (1987) contribution to this research area was to highlight the role of oxytocin-environment interactions in modulating the progress of labour.

Newton’s studies showed that mice had longer labours and fewer surviving pups in threatening environments, while subsequent research in rats confirmed that maternal oxytocin levels decrease in unfamiliar or disturbed environments, causally slowing the process of parturition (Newton et al., 1966). From an adaptive perspective, Newton proposed that the central oxytocin-mediated fetal ejection reflex functions to exhibit inhibitory control over early labour progress in potentially dangerous situations.

The ‘Odent’ fetus ejection reflex was observed in women who gave birth in undisturbed environments, and it appears to overlap with the powerful, peristaltic wave described in rabbits by Ferguson (Newton, 1987; Odent, 1987; 2009a). As labour progresses and birth approaches, Odent (1987) observed that undisturbed women experience highly intense and *involuntary* contractions that powerfully and rapidly expel the fetus, in contrast to women who voluntarily push to expel the fetus.

This fetus ejection reflex is hypothesized to be mediated by adrenalin, as when women approach this phase of parturition, they become highly fearful, muscularly powerful, and frequently refer to death or express intense emotions such as anger (Odent, 1987; 2009a). It is important to note that Odent’s observations were based on his obstetrical experiences with a large number of parturients in a birthing center; however, to the best of our knowledge, these observations have not been recorded, quantified, or analyzed in a systematic manner.

When an authentic fetus ejection reflex occurs, Odent (1987) maintains that newborns do not lose weight post-birth, perineal trauma is prevented, and that lactation reliably begins within an hour. Furthermore, the fetus ejection reflex coincides with intense emotions of joy, ecstasy, and relief felt by the birthing woman, that help her transition into motherhood (Northrup in *Orgasmic Birth;* Pascali-Bonaro, 2008). These observations clearly require verification, but the fetus ejection reflex is proposed to only occur when labour has progressed in a familiar environment, making empirical verification a considerable challenge. In terms of the function of the fetus ejection reflex,

Odent proposes that once labour progresses past a critical point, the fetus ejection reflex is adaptive for promoting rapid expulsion of the fetus.

If Odent's fetus ejection reflex were verified in women, then the genito-pelvic reflexes that mediate this involuntary response would require identification. The strong uterine muscle is likely the key driver of this reflex, but given Ferguson's description of a powerful, peristaltic wave moving from the cervix downward through the vagina in rabbits, it is possible that the deep and superficial vaginal sphincters described by Shafik (1993; 1995) and Broens et al (2014) serve the peristaltic movement of the fetus ejection reflex in human females. Furthermore, though the vagina, cervix, and uterus represent three distinct structures in terms of function, they develop from the same embryological structure (Kobayashi & Behringer, 2003), so it is possible that peristaltic and contractile activity is continuous through all three structures.

A role for vaginal sphincters in facilitating human parturition under natural conditions is at present difficult to verify, but observations of parturition reflexes in several animals makes this a reasonable hypothesis. The comparison of the two literatures suggests some asymmetry: in animals, female genito-pelvic reflex activity is usually interpreted in the context of birth while in human research, these reflexes are usually interpreted in the context of sexual pleasure, and frequently, male sexual pleasure.

Although the human female genito-pelvis evolved to serve both coital and parturition functions, very little research explicitly addresses this fact. Reflexes with original functions in fetal and placental expulsion could be activated in a coital context, especially during human intercourse, which can last for much longer periods of time than non-human coitus, due to conscious desire and purposeful ejaculation/orgasm inhibition. Could reflexes that promote fetal ejection and/or placental expulsion in a birth context contribute to 'deep' orgasm in a sexual context? Also, might activation of these reflexes in a sexual context provide benefits during labour and birth?

Birth-induced genito-pelvic injuries

Even with labour-induced biomechanical and biochemical changes to the genito-pelvis, many women still sustain injuries during birth as well as pelvic floor dysfunction following birth. Vaginal birth frequently causes perineal trauma, ranging from mild to

severe lacerations occurring as the baby exits the birth canal (Johanson, 2000). The most common kinds of pelvic floor dysfunctions predicted by vaginal birth are prolapse, which involves the slippage of organs, and incontinence, which involves involuntary release of urine or feces (Hallock & Handa 2016).

Parity is the strongest predictor of both incontinence and pelvic organ prolapse in women (Ashton-Miller & DeLancey, 2009; Hendrix et al., 2002). For example, women with one child are four times more likely to experience prolapse, and women with two children are over eight times more likely to develop prolapse than nulliparous women (Mant et al. 1997). In another review, one vaginal delivery was found to increase the odds of prolapse in later life by a factor of 9.73 (Hallock & Handa, 2016). These findings illustrate the sensitivity of the female pelvic floor to injury and dysfunction; indeed, one quarter of American women exhibit at least one type of pelvic floor dysfunction (Hallock & Handa, 2016). The impact of pelvic floor dysfunction on female fitness is difficult to quantify in modern environments, but is expected to have had negative impacts on female fitness in ancestral conditions.

Pelvic floor injuries represent structural failures, and their frequency is somewhat of an evolutionary puzzle given the negative impacts that pelvic floor dysfunction has on female health and sexual function (Bortolini et al., 2010). Having one vaginal birth increases the odds of pelvic prolapse by a factor of ten, but additional births do not significantly affect the risk (Quiroz et al., 2010). The severity and frequency of prolapse and incontinence experienced by parous women illustrates the importance of pelvic floor functionality and integrity. What kinds of factors increase the ability of pelvic floor muscles and tissue to withstand large amounts of strain? Can regular sexual activity help maintain functionality of the pelvic floor?

Pelvic floor condition, sexual functioning and birth outcomes

The condition of the pelvic floor is positively associated with sexual functioning (Rosenbaum, 2007). Pelvic floor functionality is assessed on the basis of both muscular strength, measured by strength and duration of voluntary contractions, and tone, measured by applying pressure to resting muscles and then assessing the muscle's resistance (Haylen et al., 2010). Both Kegel (1952) and Graber and Kline-Graber (1979) found that women who could regularly orgasm had stronger pubococcygeal muscles

than non-orgasmic women, but other studies found no effect of pelvic floor strength on orgasmic capacity (Chambless et al., 1982; Trudel & Saint-Laurent, 1983; Gameiro et al., 2013).

One study found that trained sexologists could accurately predict whether or not women were capable of having vaginal orgasms based on the quality of their gait; free and unblocked movement of the legs, pelvis, and spine may contribute to the ability to have a vaginal orgasm (Nicholas et al., 2008). Furthermore, women with expanded sexual response, characterized by the capacity to experience multiple and extended orgasms, demonstrate stronger pelvic floors and also self-report a heightened awareness of internal erogenous zones (Sayin, 2011; 2012).

Women with high or moderate pelvic floor strength, based on both strength and duration of voluntary muscle contractions and controlling for age and parity, reported higher levels of sexual arousal and orgasm than women with weak pelvic floors (Lowenstein et al., 2010). In the same women, the duration of voluntary pelvic contractions positively predicted levels of arousal intensity and orgasm frequency (Lowenstein et al., 2010). Martinez and colleagues (2014) also found that stronger pelvic floor muscles predicted higher levels of desire, arousal, orgasm, lubrication, and sexual satisfaction. In women with incontinence, stronger pelvic floors predicted higher levels of sexual activity and orgasm, but there was no relationship between pelvic tone and sexual activity or functioning (Kanter et al., 2015). Baytur and colleagues (2005) reported no correlation between sexual functioning and pelvic floor muscle strength in a group of postpartum women, but weak pelvic floors predicted sexual dysfunction in both pregnant and non-pregnant women in another study (Santos et al., 2017). Another recent study found that women's self-reports of sexual function correlated with pelvic floor strength, such that weaker pelvic floor muscles were associated with higher levels of sexual problems (Ozdemir et al., 2017).

Overall, these studies suggest a positive relationship between pelvic floor health and several domains of sexual functioning, but the causal direction between these variables is not fully elucidated. In a comprehensive review on genito-pelvic reflexes, Levin (2003b) proposed that frequent sexual activity enhances vaginal and pelvic floor structure and functionality through increasing blood and oxygen flow to the genitals while providing regular exercise of the complex musculature and reflexive activity of the

female pelvic floor. Consistent with Levin's account is evidence that sexually active post-menopausal women have lower levels of vaginal atrophy than non-sexually-active post-menopausal women (Leiblum et al., 1983). These theoretical and empirical lines of evidence thus indicate that sexual activity can lead to enhanced pelvic floor functioning. A reciprocal relationship between sexual and pelvic functioning is probably the most accurate, given the positive impacts of pelvic floor exercise on sexual functioning, which is reviewed below.

Research on women's pelvic floor in relationship to labour and birth outcomes largely focuses on how parturition affects postpartum pelvic floor health (e.g. Handa et al., 1996; Patel et al., 2006; Bortolini et al., 2010). One study reported that 35% of the variability in postpartum pelvic floor strength was predicted by pelvic floor strength during pregnancy, but factors influencing pelvic floor strength during pregnancy were unknown (Klein et al., 1997). Interestingly, computational models indicate that voluntary muscular contractions are less effective than involuntary smooth muscle activity at expelling a fetus, as pelvic floor muscle activation during parturition was found to *increase* resistance for the descending fetus (Parente et al., 2010). This finding suggests a role for reflexive activity in the female genito-pelvis during parturition. A deeper understanding of the factors influencing both voluntary and involuntary aspects of pelvic floor functioning prior to labour and delivery is needed.

Physical interventions that jointly impact sex and parturition

To examine the prediction that sexual activity might provide 'practice for parturition' via maintenance of the genito-pelvic musculature and reflex activity, we review findings from studies that examined effects of pelvic floor interventions on sexual response or parturition outcomes. Table 5.2 summarizes studies that assessed either sexual or birth outcomes in women following a program of pelvic floor training or genital/perineal massage. Overall, these studies indicate that similar kinds of interventions contribute to pleasurable sexual functioning, orgasmic capacity, faster labour, and reduced birth injury. It should be noted that there is a high degree of variability in the types of interventions used in these studies; Table 5.2 provides a brief review of the main effects.

Positive impacts of pelvic floor training and genito-pelvic massage on sexual functioning and birth outcomes arise through several interacting processes: increased awareness of genito-pelvic sensations (Ferreira et al., 2015; Messe & Geer, 1985); increased stretch, elasticity, and motility of genito-pelvic tissue (Leon-Larios et al., 2017); and increased pelvic floor muscle strength and tone (Ferreira et al., 2015). The psychological impacts of these interventions are not well understood but worthy of research attention. Though these interventions are generally delivered in a medical or physical therapy context, they can involve forms of stimulation that broadly overlap with various types of sexual activity.

While exercise of the pelvic floor can enhance sexual pleasure and improve birth outcomes, over-activity or hyper-tonicity of pelvic floor muscles, caused by lifestyle habits such as posture or voluntary holding of urine, contribute to sexual pain disorders and birth complications (Faubion et al., 2012; Padoa, 2016; Spoelstra et al., 2018). Indeed, Bortolami and colleagues (2015) found that women with low pelvic floor muscle tone had lower levels of sexual dysfunction. Thus, an optimally functioning pelvic floor requires that both striated and smooth muscles are capable of both full contraction and full relaxation (Padoa, 2016).

We suggest that, under the ‘practice for parturition’ hypothesis, stimulation of the genito-pelvis in a sexual context may assist in the unimpeded activity of genito-pelvic reflexes in a birth context. Niles Newton’s body of work described an oxytocin-mediated fetal ejection reflex in early labour, and we have integrated her work with current knowledge on genito-pelvic reflexes and pelvic floor function that contribute to female coital function and pleasure. In addition to the physical similarities between sex and birth, Newton also highlighted that these two reproductive processes involve emotional and psychological intensity. Next, we extend Newton’s ideas by reviewing details of the psychological connections between sexual pleasure and parturition.

Table 5.2 Effects of pelvic floor interventions on sexual functioning and labour and birth outcomes

Intervention	Effect on Sex & Orgasm	Effect on Labour & Birth Outcomes
External or internal massage of pelvis &/or genitalia	Elimination of pain during sex (n = 18) & significant increase in desire, arousal, lubrication, orgasm, & satisfaction (n = 8) in women experiencing dyspareunia (painful sex)[1] Increased orgasms & decreased pain after receiving external abdominal & pelvic massage to reduce scar tissue (n = 23)[6] Vaginal acupressure (combination of internal massage & verbalization of sensations) improved subjective sexual ability in women experiencing pain during sex (n = 6) & for women experiencing lack of desire or orgasm (n = 6)[11]	Fewer third degree tears in group randomly assigned to practice perineal massage during second trimester. No group differences (n = 1340) in rates of intact perineums or first or second degree tears[10]
Pelvic floor training - a regular practice involving voluntary contractions of pelvic floor muscles	Systematic review of 8 randomized control trials concluded that most studies reported improvement in at least one sexual domain in intervention group relative to control group[4] Subjective ratings & physiological measures of arousal (vaginal vasocongestion) increased in intervention group (n = 10)[5]	Lower rate of prolonged 2nd stage of labour in training group (n = 120) relative to control group (n = 153)[3] Training during pregnancy prevented urinary incontinence 6 months after parturition[7] No significant differences between control & intervention groups[8] Meta-analysis of 12 studies showed training reduced duration of 1st & 2nd stage of labour in primigravida[9] Meta-analysis of 16 studies found that pelvic floor exercise reduced duration of 2nd stage of labour & reduced severe perineal trauma[12]
Internal (vaginal & perineal) massage & pelvic floor training		Reduced analgesia usage, shorter 2nd stage labour, higher frequency of intact perineum, fewer episiotomies, & fewer severe perineal tears in intervention group (n = 254) relative to control group (n = 212)[2]

References: 1) da Silva et al 2017; 2) Leon-Larios et al 2017; 3) Salvesen & Mørkved 2004; 4) Ferreira et al 2015; 5) Messe & Geer 1985; 6) Wurn et al 2004; 7) Boyle et al 2014; 8) Dias et al 2011; 9) Du et al 2015; 10) Stamp et al 2001; 11) Ventegodt et al 2006; 12) Sobhgol et al 2020

5.6.2. Psychological links between sex and parturition

Newton (1973/1992) drew a parallel between sexual arousal/orgasm and labour/birth in that psychic inhibitions or blockages can be released during both activities. Indeed, sex and parturition both involve psychological experiences that are qualitatively distinct from 'normal' or everyday modes of thinking and feeling. Under the 'practice for parturition' hypothesis, we assume that psychological states typically occurring during sex and birth are adaptive, and we predict that regular sexual activity increases the accessibility of psychological states that facilitate birth.

To evaluate these predictions, we conducted a comprehensive literature search for articles assessing relationships between psychological traits and sexual response, as well as psychological traits and parturition outcomes, in women, using key word combinations such as "personality" and "orgasm", and "personality" and "parturition". We examined references and citations of relevant articles and also searched within articles citing the widely used Female Sexual Function Index (FSFI; Rosen et al., 2000) for articles that examined sexual response in relationship to psychological or personality characteristics. Our findings are organized in the following way: we first describe how the capacity to surrender cognitive and bodily control is beneficial in both sex and birth contexts; second, we review a constellation of psychological constructs that reflect the capacity to surrender cognitive control; third, we describe how this capacity to surrender control, as reflected in various overlapping traits and states, predicts sexual functioning and; fourth, labour and birth outcomes.

Surrender of cognitive control in birth and sex

Sex, especially orgasm, and childbirth are known elicitors of profound and meaningful alterations to consciousness; during these processes, women can experience dramatic changes in the way they perceive time, space, their bodies, and their sense of self (Parratt & Fahy, 2003; Castro, 2010; Sayin, 2011; Sayin, 2012; Costa et al., 2018). When women face labour and childbirth, they are confronted with a novel and unpredictable challenge that cannot be cognitively solved, given the central role of automatic bodily processes in parturition.

Engagement of complex cognitive processes such as linguistic communication and self-reflection can actually hinder the process of parturition by interfering with a

woman's ability to focus on the intense bodily task of giving birth (Odent, 2009a). Similarly, distracting thoughts and mind-wandering during sexual activity tend to reduce or inhibit sexual arousal and desire in women (Brotto et al., 2016; Carvalho & Nobre, 2010). The tendency of thought, language, and self-reflection to interfere with sexual arousal, orgasm, labour, and birth can be conceptualized as a tension and tradeoff between higher-order cognitive processes and evolutionarily-older physiological processes. Thus, psychological states that facilitate sexual pleasure, orgasm, and parturition should involve shifts in thinking and feeling that promote or allow uninhibited and automatic activity of the genito-pelvis.

The importance of permitting a bodily process to unfold is clearly observable in women's sex and birth experiences, as descriptions of both activities involve the theme of 'letting go' or 'surrendering' (Parratt & Fahy, 2003; Birnbaum et al., 2006; Ménard, 2007; Pfaus et al., 2016; Karadi, 2011). For example, during sex, women report a stronger psychological need to 'let go' compared to men (Birnbaum et al., 2006). Women who easily experience coital orgasms describe a greater loss of bodily control during orgasm compared to women who have difficulties reaching orgasm during coitus (Bridges et al., 1985). Further, detailed descriptions of pleasurable and highly rewarding sex emphasize the role of presence and immersion within the sexual experience, in sharp contrast to thinking about or analyzing the experience (Ménard, 2007).

This tension between cognitive processes that underpin 'normal' or 'everyday' behaviour and bodily processes that unfold automatically is particularly evident in labour and birth contexts:

> The process of 'releasing the body' occurs spontaneously and progressively throughout labour, but it is easily disturbed and is not simple to achieve because such a total bodily release is necessary. These difficulties are related to the self-control that is necessary to function in the social world, yet which needs to be released entirely to give birth spontaneously and naturally. (Parratt & Fehy, 2003, p. 6)

Given the important role of genito-pelvic reflex activity in sex and birth, and based on women's accounts of the need to 'let go' in these contexts, we suggest that the capacity to surrender cognitive control over a bodily process is a conditionally-adaptive psychological feature that facilitates pleasurable sex, orgasmic capacity, labour, and birth. Evidence from brain imaging research supports this interpretation, as some studies

report sex-related deactivation of frontal and midline cortical regions that serve self-reflective and executive functioning, providing a neurological underpinning for the 'loss of control' that is central to the experience of orgasm (Georgiadis & Kringelbach, 2012; Georgiadis, Kringelbach & Pfaus, 2012; Safron, 2016).

Constellation of traits related to surrender of control

There are multiple, overlapping psychological constructs that involve the capacity to surrender cognitive control via focused attention and reduced analytical or self-reflective thought. Trait absorption describes a person's tendency to become deeply focused upon and immersed within an experience, such as a daydream, visual stimulus, task, or sensation (Tellegen & Atkinson, 1974; Jamieson, 2005). Absorption is frequently used as a proxy for the imaginative and sensory dimensions of the personality trait of openness to experience, which encompasses imagination, creativity, and interest in art (DeYoung et al., 2012).

Overlapping with trait absorption is a person's level of responsiveness to being hypnotized, which generally involves a set of instructions intended to increase the person's attention and focus on particular stimuli (Cardeña & Terhune, 2014). Though findings on the neural mechanisms underlying sensitivity to hypnosis and hypnotic states are highly variable (Landry, Lifshitz, & Raz, 2017), hypnosis does appear to involve the inhibition of cognitive functions such as willed action, critical self-reflection, memory accessibility, and logic (Ott, 2007), which is consistent with our framing of this trait as involving the release of cognitive control. Furthermore, hypnotic suggestibility predicts a wide range of sensory and cognitive predilections, including the tendency to experience altered states of consciousness (Cardeña & Terhune, 2014).

A third related trait is self-transcendence, a construct that describes how strongly someone feels a sense of connectedness to life (Cloninger et al., 1993). Self-transcendence positively predicts a person's tendency to describe themselves as spiritual and to report having spiritual experiences (MacDonald & Holland, 2002). A facet of self-transcendence is creative self-forgetfulness, the tendency to become deeply involved in sensory and imaginary experiences to the point where the subjective and continuous sense of self and time appears to dissolve (Cloninger et al., 1993). Creative self-forgetfulness and trait absorption clearly overlap in their definitions and scope.

Further, self-transcendence positively correlates with openness to experience and hypnotizability (De Fruyt et al., 2000; Levenson et al., 2005; Cardeña & Terhune, 2014).

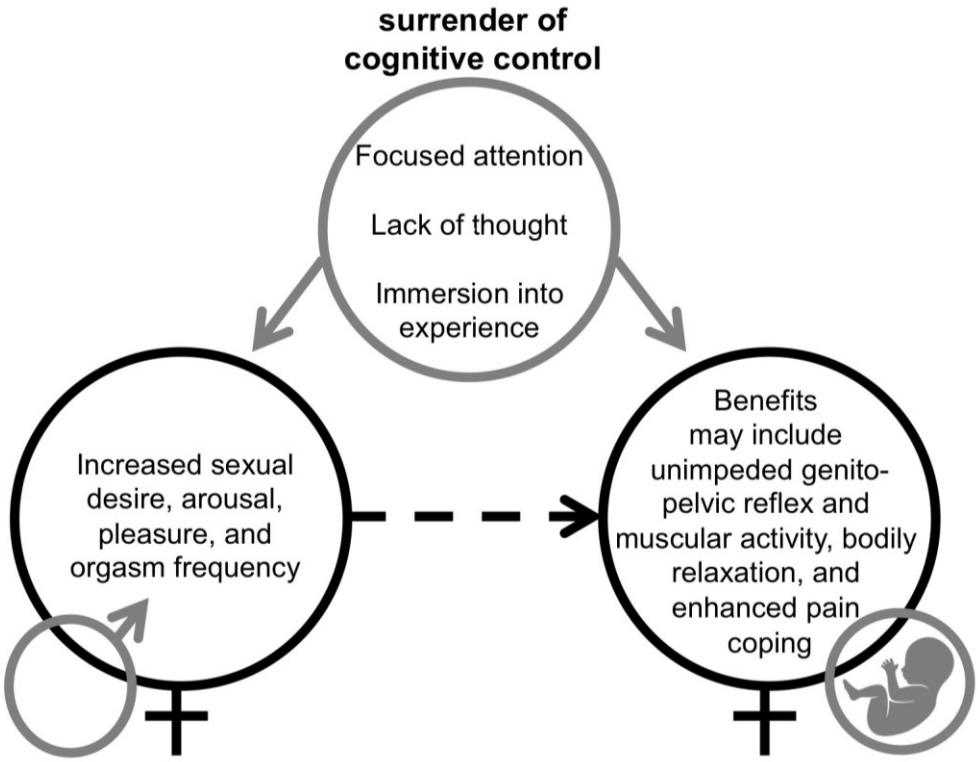
These constructs of absorption, openness, hypnotic suggestibility, self-transcendence, spirituality, and creative self-forgetfulness are measured with different types of instruments and each has its own extensive body of literature outlining their nature and correlates. All of these constructs describe a psychological tendency to directly experience objects of attentional focus in a nonconceptual manner (Cardeña & Terhune, 2014). A key theme weaving through this trait constellation is the ability or propensity to deeply focus attention upon an internal image or sensation or an external stimulus, which coincides with reduced or absent self-reflective thought as well as reduced attention toward distracting stimuli.

Under our hypothesis we expect that women with higher levels of these traits experience more frequent and more intense sexual arousal and orgasms as well as briefer labours and fewer birth-related injuries (Figure 5.4). We also expect that women who practice these kinds of focused attention states will demonstrate enhanced sexual functioning and better birth outcomes.

Surrender of cognitive control and sexual functioning

The capacity to surrender cognitive control, as assessed through several interrelated psychological constructs, has clear, positive associations with multiple aspects of female sexual response and behaviour (Figure 5.5). Interestingly, Swartz (1994) hypothesized that absorption constitutes an obligatory pathway for high desire and sexual arousal in women but not for men. Several findings are consistent with this hypothesis. For example, spirituality, especially the yearning to feel connected, demonstrates positive associations with several facets of female sexuality, including frequency of unprotected vaginal sex and number of sex partners, while male spirituality had no effect or a negative effect on these variables (Burris et al., 2009).

Figure 5.4 The capacity to surrender cognitive control promotes sexual pleasure and appears to have positive effects on labour and birth



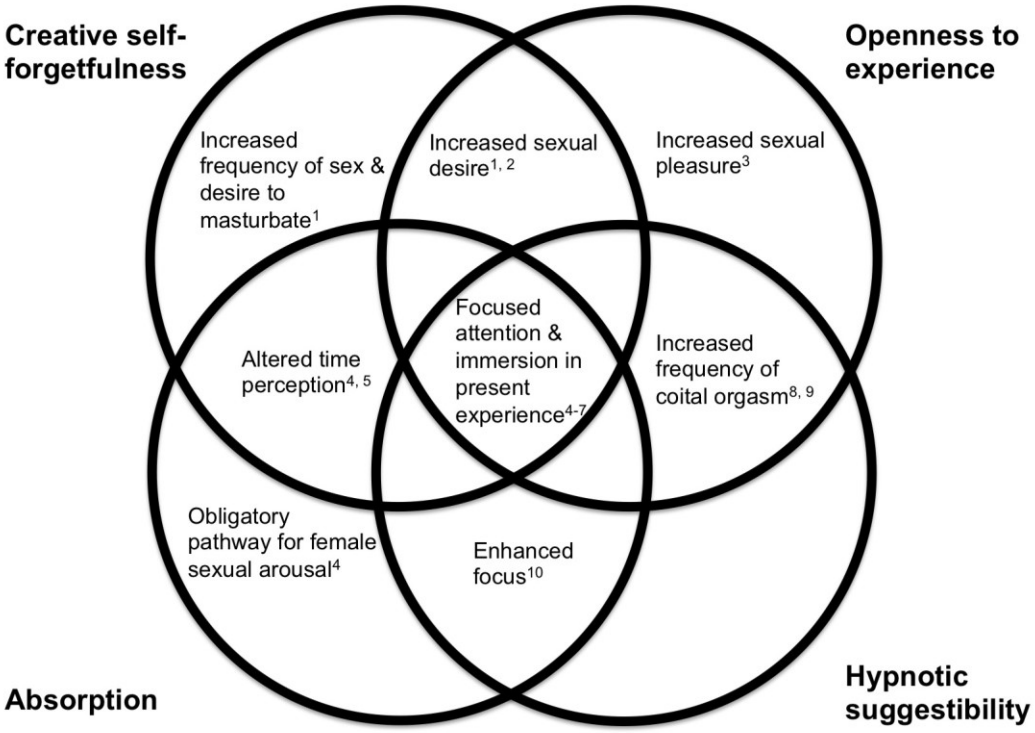
The dashed arrow represents our hypothesis that experiencing 'surrendered' states in sexual contexts increases the accessibility of those states in parturition contexts.

Openness to experience positively predicts multiple aspects of sexual functioning in women but not men, including sexual desire, sexual pleasure, and coital orgasm frequency (Birnbaum & Gillath, 2006; Harris et al., 2008; Costa et al., 2016a). Similarly, creative self-forgetfulness demonstrates positive associations with sexual desire, non-coital sex frequency, and desire for masturbation in women (Costa et al., 2016a; Costa et al., 2018). Women who are more prone to hypnotic suggestion report higher levels of orgasm during sexual intercourse compared to women who are not susceptible to hypnosis (Bridges et al., 1985).

Heightened bodily awareness enhances sexual pleasure in both sexes, while focused attention upon genital sensations appears to play a particularly important role in women's pleasure and orgasmic capacity (Costa et al., 2016b; Sayin, 2011; Brody & Weiss, 2010). Bodily and genital sensations can become a stimulus to which focused

attention is directed, so the positive relationship between genital awareness and orgasmic capacity may involve absorption.

Figure 5.5 The interrelated psychological traits and states of creative self-forgetfulness, openness to experience, absorption, and hypnotic suggestibility



These traits overlap with one another in promoting focused attention on a given stimuli, and each of these traits shows associations with female sexual response and sexual behaviours.

References: 1) Costa et al 2018; 2) Costa et al 2016a; 3) Birnbaum & Gillath 2006; 4) Swartz 1994; 5) Cloninger et al 1993; 6) DeYoung et al 2012; 7) Crawford et al 1993; 8) Harris et al 2008; 9) Bridges et al 1985; 10) Kallio & Revonsuo 2003

Positive associations between this trait constellation and female sexual pleasure demonstrate that psychological facilitators of women's sexual functioning specifically involve the surrender of cognitive control via increased focus and attention, lack of conscious thought, and immersion into an experience (Figure 5.5). Under the 'practice for parturition' hypothesis, we predict that the pleasure associated with sexual activity positively reinforces the capacity to surrender cognitive control, such that a greater capacity to release bodily inhibitions during sex makes such a state more highly accessible during later parturition (Figure 5.4).

Surrender of cognitive control and parturition

Only a few studies have examined the traits outlined above in relationship to parturition outcomes; however, various qualitative descriptions of women's birth experiences reveal a central role for surrendering cognitive control. Low levels of openness to experience predict a greater need for assisted delivery in one study (Johnston & Brown, 2013) and positive impacts of various hypnosis techniques on birth outcomes have been reported in several studies.

First, women are significantly more susceptible to hypnosis in the third trimester of pregnancy relative to non-pregnancy (Alexander, Turnbull, & Cyna, 2009), suggesting that cognitive correlates of a hypnotic state are more accessible as pregnancy progresses. In a meta-analysis on three randomized control trials, where pregnant women were randomly assigned to hypnosis training or to a control condition, Cyna and colleagues (2004) found that learning hypnosis techniques during pregnancy predicted lower subjective levels of pain and reduced usage of pharmacological analgesia. Another review concluded that hypnosis training has positive impacts on birthing women in terms of reducing pain levels as well as duration of labour (Brown & Hammond, 2007). Recent systematic reviews came to somewhat different conclusions, as Jones and colleagues (2012) found insufficient evidence that hypnosis worked better than a placebo for pain in birth, while Madden (2016) found that women learning hypnosis were less likely to use pharmacological analgesia.

In a sample of pregnant teenagers, Martin and colleagues (2001) found that random assignment to hypnosis training predicted fewer complicated deliveries and surgical procedures relative to supportive counseling. Similarly, Mehl-Madrona (2004), found that women who received training in hypnosis had significantly fewer complications during delivery compared to women assigned to a psychotherapy condition. In contrast, multiple studies have failed to find an impact of hypnosis training on birth outcomes, which may be due to high variability in individual susceptibility to hypnosis and hypnosis techniques. (Werner et al., 2013a; Werner et al., 2013b; Cyna et al., 2013). Beevi, Low, and Hassan (2017) found that women receiving a hypnosis intervention had fewer epidurals but more assisted vaginal deliveries than women receiving routine antenatal care, plus infants of mothers from the intervention group had non-significantly higher Apgar scores (Apgar scores assess the physical condition of a

neonate). Together, these studies indicate that hypnotic training can have positive impacts on parturition.

Qualitative, cross-cultural research reveals that women across cultures recognize the importance of needing to 'go with the flow' when it comes to experiencing the powerful and uncontrollable physiological processes of labour and birth (Namey & Lyerly, 2011; O'Donnell, 2004; Newton & Newton, 2003). A large body of studies from the parturition literature report that women describe themselves as entering 'the zone' during labour and birth, which is characterized as a psychological space of intense inner focus involving altered perceptions of time and space (Dixon et al., 2013); these descriptions of 'the zone' clearly overlap with descriptions of trait absorption and self-transcendence.

Anthropological evidence further demonstrates the role of attentional absorption in parturition. Usage of sensory stimuli such as visual art, sound, and scent to facilitate birth and pain coping during labour is a common practice in traditional societies around the world (Newton & Newton, 2003, p. 20). While these practices appear to assist women in attaining a deeper level of singular focus, the ability of focused attention upon internal versus external stimuli to impact a woman's birth experience requires further clarification.

Under the 'practice for parturition' hypothesis, we predict that women who are capable of reaching deeper levels of absorption and immersion during sexual activity have an easier time having a natural birth, as they are better able to mentally focus on the task at hand and more capable of allowing their bodies to surrender to the physiological processes governing birth. To further clarify the role of surrendering cognitive control in labour and birth, future studies could examine trait and state absorption and its overlapping constructs in relationship to parturition outcomes.

5.7. Evaluating the 'practice for parturition' hypothesis

If sexual activity functions, in part, as practice for parturition, then sexual variables should predict aspects of birth. There exists a small body of research on the impacts of pre-parturition sexual activity on labour and birth outcomes (Table 5.3). Though most of this work was conducted to assess whether or not sexual intercourse

during late pregnancy hastens the onset of labour, the results are relevant to our hypothesis.

5.7.1. Effects of pre-parturition sex on labour outcomes

As Table 5.3 shows, several studies found that at-term sexual intercourse promotes labour onset, reduces the duration of labour, and reduces the need for interventions such as induction or instrumental delivery. Baxter (1974) found that a woman's self-reported capacity to have coital orgasms prior to conception predicted a briefer mean second stage of labour ($\bar{x}$ = 41 minutes) compared to women who did not have coital orgasms prior to conception ($\bar{x}$= 70 minutes). However, Baxter (1974) did not report the standard deviations of these data, making significance tests of group mean differences impossible (Wagner & Pavličev, 2017). Though this reduction in the duration of the second stage of labour has been criticized as clinically insignificant (Wagner & Pavličev, 2017), interventions such as caesarean deliveries and injuries such as perineal trauma significantly increase in likelihood when the second stage of labour exceeds 60 minutes (Cheng et al., 2004). This possible link between coital orgasms and labour duration needs to be replicated.

That sexual variables such as pre-pregnancy orgasmic capacity and at-term sexual activity are predictive of better labour and birth outcomes strongly suggests that sexual stimulation prepares women's bodies for childbirth, which is also consistent with observations from experienced midwives (Gaskin, 2003). Salient to our hypothesis is uncovering the mechanisms through which orgasm and sexual activity prior to and during pregnancy impact the course of parturition. Possible mechanisms might include frequent genital lubrication, stretching and oxygenation of vaginal and perineal tissues, and strengthening and toning of pelvic floor muscles. Overall, the studies described in Table 5.3 provide preliminary support that sexual intercourse and orgasm may improve labour and birth outcomes, though the ways in which sexual activity impacts parturition require clarification.

Table 5.3 Effects of sexual activity and/or orgasm during pre-pregnancy and pregnancy on labour and birth outcomes

Category	Outcome	Effect of sexual intercourse	Effect of orgasm
Onset of labour	Spontaneous onset	At-term coitus had no effect on labour onset in two studies[1, 2], extended onset of labour in one study[3], and reduced onset of labour in one study[6]	No effect on labour onset[3] Possible association with prematurity[9]
	Gestational age (GA)	At-term, sexually active pregnant women had lower GA than abstaining women[4]	
	Post-due-date	At-term, sexually active pregnant women had fewer post-due-date births[5, 6]	
Progression of labour	Normal labour*	At-term, sexually-active pregnant women more likely to have normal labour & spontaneous** delivery[7]	
	Duration of 2nd stage of labour	At-term, sexually-active pregnant women were more likely to have a 2nd stage of labour lasting ≤ 30 minutes[7]	Pre-pregnancy coital orgasms predicted reduced duration of 2nd stage of labour in primiparas[8]
Interventions	Forceps		Pre-pregnancy coital orgasms predicted reduced forceps usage in primiparas[8]
	Induction	At-term, sexually-active pregnant women required less oxytocin[7] and fewer inductions[5, 6]	Pre-pregnancy coital orgasms predicted reduced use of oxytocin in primiparas[8]
	Caesarean delivery	At-term, sexually-active pregnant women had fewer caesarean deliveries[7]	

*Normal labour is inferred from partograph readings that assess numerous variables including fetal heart rate, rate of cervical dilation, fetal head descent, and contractions. When cervical dilation is progressing more slowly than clinicians prefer, and medical action is deemed necessary, the labour is no longer categorized as normal.

**Spontaneous delivery means that the woman did not require or undergo an episiotomy or instrumental or caesarean delivery.

References: 1) Schaffir et al 2006; 2) Tan et al 2007; 3) Tan et al 2009; 4) Atrian et al 2015; 5) Sekhavat & Karbasi 2010; 6) Tan et al 2006; 7) Foumane et al 2014; 8) Baxter 1974; 9) Wagner et al 1976

5.7.2. Effects of pre-parturition sexual dysfunction on labour outcomes

If frequent and pleasurable sexual activity positively impacts labour and birth, then does sexual dysfunction negatively impact labour and birth outcomes? This is a logical question to pose, though in spite of the high prevalence of female sexual dysfunction, there exist very few studies measuring the influence of sexual dysfunction on parturition. Here we briefly review forms of female sexual dysfunction and their associations with labour and birth outcomes.

Sexual dysfunction is a broad category encompassing multiple diagnoses that centrally involve sexual difficulties due to pain, low libido, or other interacting causes (Rosenbaum & Padoa, 2012). Vaginismus involves involuntary muscle spasms of the vaginal introitus and affects up to 5% of women; attempts to engage in penetration can lead to intense pain and frustration in women coping with this condition (Rosenbaum & Padoa, 2012). Dyspareunia affects up to 20% of women and involves painful sexual intercourse while vulvodynia describes genital pain with unclear causes (Leeners et al., 2015; Padoa, 2016).

In a large population based study, women with vaginismus were more likely to have experienced infertility, labour induction, vacuum delivery, and cesarean delivery compared to women without vaginismus (Goldsmith et al., 2009). Another study found that women with vulvodynia were more likely to deliver via caesarean section (Nguyen & Harlow, 2009). These results require replication but indicate that some forms of sexual dysfunction are negatively associated with labour and birth progress.

The link between sexual dysfunction and parturition problems may be partly attributable to the inability of women with sexual pain disorders to relax their pelvic floor muscles and to allow their perineum to soften during labour and delivery (Rosenbaum & Padoa 2012). How other types of sexual dysfunction, such as chronically low sexual desire, influence parturition is currently unknown. Under the ‘practice for parturition’ hypothesis, it is expected that women with various forms of sexual dysfunction experience challenges during labour and birth, whether this is due to physical causes such as those outlined above, or psychological causes, such as the inability to ‘let go’.

5.8. Do cervical orgasms involve birth mechanisms?

Next we investigate the hypothesis that cervical orgasms involve activation of labour and birth mechanisms in a sexual context. At least two researchers have mentioned this possibility, but the idea has yet to be formalized as a hypothesis for explaining orgasm in women. We first describe the cervix and the challenges in studying cervical orgasm. Second, we describe how features of cervical orgasm can be understood in the context of oxytocin release and vagus nerve stimulation. Third, we examine parturition mechanism candidates that may be involved in cervical orgasm, including the Ferguson reflex and vaginocervical stimulation-induced analgesia. Finally, we outline other similarities between aspects of parturition and cervical orgasm.

The cervix is cylindrically shaped and located at the bottom of the uterus, providing a gateway between the vaginal canal and the uterus, allowing the passage of menstrual fluid, semen, and a fetus. During sexual arousal, the cervix lifts up and away from the upper vagina as part of the vagino-levator reflex, as described above. During pregnancy, the tough fibrous nature of the cervix holds the fetus in the uterus and during labour, the cervix softens and dilates through a combination of chemical changes and oxytocin-mediated uterine contractions (Myers & Elad, 2017). These various functions of the cervix are mediated in part through three sensory nerves: the pelvic nerve, hypogastric nerve, and vagus nerve (Komisaruk & Sansone, 2003). Innervation by three different nerves (other genital structures are innervated by one or two nerves) may highlight the evolutionary significance of cervical functions, as neural redundancy insures that sensory input from the cervix reaches the brain to elicit key reproductive reflexes (Nemati & Weitkamp, 2020).

There are significant challenges in studying cervical orgasm. Firstly, it is difficult to know whether or not cervical stimulation alone results in orgasm in naturalistic settings, as sexual activity generally involves both direct and indirect stimulation of numerous genital regions simultaneously. Secondly, researchers use different definitions such as ‘coital’ or ‘vaginal’ orgasm, which may or may not involve cervical stimulation. With these caveats in mind, we place cervical orgasms within the category of ‘deep’ orgasm, and draw on research from this area.

As described in detail above, ‘deep’ orgasms generated from stimulation of the upper vagina and/or cervix have a sensation of coming from within the body, tend to occur during partnered sex, involve more ‘whole body’ sensations, involve significant alterations to one’s sense of time, space, and self, and have analgesic properties. The altered states of consciousness and deep, whole body sensations associated with cervical stimulation are likely consequences of vagal nerve stimulation. Of genital structures stimulated during sexual activity, only the cervix transmits information via the vagus nerve and because the vagus nerve transmits visceral sensations to the brain, the quality of experience from vagal stimulation may produce a distinct dimension of pleasure for women, which is consistent with women’s qualitative reports of effects of cervical stimulation (Nemati & Weitkamp, 2020).

Cervical stimulation and deeper vaginal penetration resulting in orgasm involves a greater duration of immobility and physical as well as psychological vulnerability, presumably resulting in elevated oxytocin release. To the best of our knowledge, quantity of oxytocin release during clitoral or external genital stimulation has yet to be compared with quantity of oxytocin release during cervical stimulation. Such a comparison may be difficult as vaginocervical stimulation can indirectly stimulate buried clitoral structures (Levin, 2015), but under the present hypothesis, it is expected that cervical stimulation and resultant orgasm involve elevated oxytocin levels compared to orgasms elicited from external stimulation only.

Elevated oxytocin release over an extended period of time may contribute to the psychological features of ‘deep’ orgasm. Spiritual feelings, or a sense of being deeply and meaningfully connected to existence, involve the oxytocin system (Van Cappellen, Way, Isgett et al., 2016; Holbrook et al., 2015), and such experiences are part of cervical stimulation according to some women (Nemati & Weitkamp, 2020). Plasma oxytocin levels positively predict subjective orgasmic intensity, at least in women who experience multiple orgasms (Carmicheal et al., 1987). We suggest then, that cervical orgasm involves a greater duration of immobility, leading to increased oxytocin release relative to other forms of sexual contact, which results in greater subjective intensity of resulting orgasm.

Oxytocin release during labour occurs via activation of mechanoreceptors in the cervix and uterus that respond to stretch and pressure caused by fetal descent

(Ferguson reflex; Komisaruk & Steinman, 1986). Drawing from studies with human females as well as female rats, Komisaruk and Sansone (2003) conclude that vaginocervical stimulation releases oxytocin into both the plasma and spinal cord and has both parasympathetic and sympathetic nervous system effects. Though vaginocervical stimulation outside of a parturition context can induce central oxytocin release, cervical stretch is the most potent elicitor of the Ferguson reflex (Komsaruk & Steinman, 1986). It appears that the Ferguson reflex, which is a parturition reflex, can be at least partially activated during sexual contact if the upper vagina and cervix are stimulated, contributing to some of the features observed in 'deep' orgasm, such as analgesia.

Research designs that illuminated the analgesic properties of cervical orgasm as well as the role of the vagus nerve in transmitting sensory data from the cervix to the brain employ unnatural stimuli to test hypotheses (cushioned plastic cylinder; Komisaruk & Whipple, 1984; Whipple & Komisaruk, 1985). These instruments, while unlikely to mimic natural human penile-vaginal intercourse, did demonstrate that cervical self-stimulation experienced as pleasurable specifically induces an analgesic effect. Komisaruk and Sansone (2003) suggest that analgesia produced by vaginocervical stimulation may function in both coital and parturition contexts, as reduced pain and/or increased pleasure during sex and birth could facilitate bonding with mates and neonates (p. 248).

There is ongoing disagreement over whether or not the upper vagina and cervix are regularly stimulated during heterosexual intercourse (Levin, 2015). Because the cervix lifts during female sexual arousal, the deep vagina and cervix may not receive consistent stimulation during sexual intercourse, though variability depending on a woman's body and her sexual partner should also be considered (Levin, 2012, 2015). With respect to hypotheses proposing a conceptive function of 'deep' orgasm, it seems improbable that stimulation of a genital region not easily or consistently reached during heterosexual intercourse would be crucial to activate key mating adaptations such as conception with a fit partner or important psychological benefits (Levin, 2015). Based on this logic, Levin (2015, p. 349) writes, "in regard to the cervix, what has been completely overlooked is that the cervical neural links to the brain probably have no involvement in sexuality per se but rather involvement in the physiological mechanisms of parturition."

Taken together, cervical innervation via the vagus nerve, the analgesic and oxytocinergic effects of cervical stimulation, and the shape of the female genital tract during coitus, indicate that parturition mechanisms may underlie cervical orgasm in women.

Some of the evidence for a conceptive function of 'deep' orgasm is subject to interpretation. For example, women in King and Belsky's (2012) study reported that 'deep' orgasms involve 'sucking' sensations, which the authors interpreted as consistent with a sperm transport function. However, 'sucking' sensations might feel indistinguishable from 'expulsive' sensations, and perhaps respondents would select that response if given the option. Expulsive sensations emerging from the cervix might be due to the cervical capacity to dilate for fetal passage.

The process of dilation is part of cervical ripening, which involves all chemical and physical changes to the cervix as labour approaches and progresses. A key chemical factor that initiates cervical ripening is nitrous oxide (NO), which is produced by the cervix during labour. Estrogen-mediated production of endothelial NO throughout the genito-pelvis drives blood flow, vasodilation, and genital engorgement during sexual arousal in women (Musicki, Liu, Lagoda et al., 2009). Production and effects of NO on the vagina are tissue and region specific, and whether or not the cervix produces or responds to NO during sexual arousal appear unknown. Might arousal-elicited NO release in a sexual context act upon the cervix, creating an attenuated version of cervical dilation and its associated sensations? Furthermore, a parallel might be drawn between the psychological intensity of the transition phase of labour (Olza, Leahy-Warren, Benyamini et al., 2017), when the cervix is at maximum dilation, and the reported intensity of orgasms elicited from cervical stimulation.

Finally, an important aspect of orgasmic response in women is the human capacity to choose to engage in sexual activity and intercourse for extended periods of time. Doing so, in a heterosexual context, requires intentional ejaculation/orgasm inhibition, and can involve purposeful building of desire and sexual arousal through skillful technique. These capabilities permit women and their sexual partners to actively seek out the pleasurable nature of cervical stimulation, and in doing so, 'exploit' psychological and physiological mechanisms that may have evolved to serve parturition.

5.9. Discussion

Niles Newton described women's sexuality as diverse and elaborate, which she attributed to an evolutionary history of participation in three reproductive partnerships that share underlying psychophysiological mechanisms. We have extended Newton's ideas in five main ways: (1) contextualized female sexual pleasure as centrally involving oxytocin-associated *immobility without fear*; (2) reviewed the known and unknown roles of genito-pelvic reflexes in sex and parturition; (3) characterized the psychological similarities between sexual arousal, orgasm, labour, and birth; (4) introduced the 'practice for parturition' hypothesis to propose that women's capacity to experience prolonged sexual arousal, highly-expressed orgasm phenotypes, and altered modes of thinking and feeling during sexual activity provide physical and psychological preparation for future childbirth (Figure 5.2); and (5) examined cervical orgasm as an outcome of labour and birth mechanisms activated in a sexual context. Together, these explorations demonstrate the depth, utility, and generativity of Newton's framework for understanding women's capacity to experience extensive sexual pleasure.

Although oxytocin's regulation of sex, birth, and lactation is well known, its joint effects upon these three partnership elements have yet to be considered as relevant to evolutionary accounts of female orgasm. Niles Newton's framework, and our additions, offers two important shifts in thinking. Firstly, we suggest that the object to explain is not female orgasm as an isolated phenotype (the approach favoured by Lloyd, 2005), but rather the female capacity for extensive sexual pleasure, or expanded sexual response, which involves prolonged sexual arousal, no refractory period, elaborate and diverse orgasm phenotypes, and altered psychological states. We view these pleasure capacities as interrelated in terms of their influence on pelvic floor integrity and female psychology. Second, we contextualize extensive sexual pleasure as a capacity shaped by neuroendocrine, physical, and psychological mechanisms that reward and promote intimacy during costly and potentially painful aspects of female reproduction, lending phenotypic similarities between sex and birth. These two shifts represent important departures from hypotheses that use orgasm-associated oxytocin release to postulate purely singular functions of female orgasm, such as bonding or oxytocin-mediated sperm transport. Furthermore, the presence of oxytocin-mediated reflexes in arousal, orgasm, birth, and lactation (Odent, 2009b) dovetails with recent work in sexuality research that

suggests genital orgasm is a specific example of the nervous system's generalized capacity to orgasm (Komisaruk & Rodriguez del Cerro, 2021).

Studies of the human female genito-pelvis have largely focused on reflexes serving sexual arousal and coitus, leaving many unknowns concerning genito-pelvic reflexes in human birth. This lack of integration between sexuality research and parturition research echoes Newton's critiques of male-centrism in studies of female reproductive biology, and represents a key area where knowledge of sex-birth phenotypic overlap could be expanded. Multiple lines of evidence converge to indicate that regular genital stimulation and pelvic exercise maintain the functionality of the female pelvic floor, which could help explain women's capacity for fluid and prolonged sexual arousal and even the absence of a refractory period. Such a perspective suggests adaptive benefits of pleasure to women's reproductive life that extend beyond conceptive contexts and reinforcement of pair bonds.

The capacity to surrender cognitive control appears to facilitate both pleasurable sex and unimpeded parturition. Oxytocin-mediated alterations to states of thinking and feeling during sexual arousal and elaborate orgasms are of particular interest, as extended periods of immobility and vulnerability are expected to elicit greater oxytocin release and corresponding anti-stress effects. Psychological characteristics influenced by the oxytocin system that specifically impact female sexual response, such as spirituality and self-transcendence, have yet to be comprehensively integrated into evolutionary accounts of female sexual response. The relative contributions of individual personality traits versus partner characteristics in affecting female sexual pleasure and orgasm phenotypes could be explored to compare alternative hypotheses for female orgasm. Furthermore, how these psychological characteristics overlap with, and influence birth psychology as well as pain coping, require more investigation.

Under the 'practice for parturition' hypothesis, sex-birth similarities involve functional connections whereby engaging in regular and varied pleasurable sexual activity provides benefits during parturition through maintaining genito-pelvic reflexive function and making cognitive surrender more accessible (Figure 5.2). At present, a small body of limited studies support practice for parturition, suggesting that sexually active, pregnant women demonstrate briefer labours and reduced need for interventions during birth. We provide suggestions for data collection and studies to provide further

tests of our hypothesis in Table 5.4. Importantly, the 'practice for parturition' hypothesis has direct and practical implications for supporting women in preparing for labour and parturition, as well as theoretical implications for understanding the evolutionary causes underlying women's sexual response.

Future work might also clarify the relative contributions of, and interactions between, male-female mating dynamics and demands of parturition on shaping aspects of female sexuality. If the capacity to experience more sexual pleasure facilitates childbirth, then males may be attracted to women who signal greater sexual openness, so these two hypotheses need not be mutually exclusive. Furthermore, our hypothesis could contribute to explaining the presence of extended sexuality, particularly sex during pregnancy, and sexual fluidity, including same-sex intimacy, in women.

Newton described women as having a varied sexual heritage, and we suggest that cervical orgasm may represent a specific example of how parturition mechanisms expand the boundaries of female sexual pleasure. This idea might be further examined through applying the 'practice for parturition' hypothesis: do women who report cervical pleasure and/or orgasm demonstrate shorter periods of cervical dilation? Table 4 provides multiple ways of testing the idea that cervical orgasm involves parturition mechanisms. We hope to have laid some groundwork, inspired by Newton and following the work of both Levin (2015) and Komisaruk and Sansone (2003), in terms of understanding what cervical orgasm represents in the broader context of female reproductive biology.

Of Newton's sex-birth-lactation interrelationships, we have focused upon and extended her work on the sex-birth interrelationship specifically; the sex-lactation interrelationship deserves the same research attention. Indeed, Komisaruk and colleagues (2011) discovered that nipple stimulation of women maps onto the same part of the sensory cortex activated by clitoral stimulation. This finding confirms Newton's (1973/1992) characterization of breastfeeding as sensuous, and provides mechanistic insights into how lactation is reinforced, which may also explain how 'breast sex' entered the human sexual repertoire (Levin, 2006). Comparative research on the effects of genital and nipple/breast stimulation on the sensory cortex is needed to further understand similarities and differences between humans and non-human mammals

concerning the pleasure mechanisms that reinforce lactation, and how these impact female sexual responses.

Evolutionary accounts of female sexuality have largely viewed genital orgasms occurring during sexual intercourse with males as the phenomenon to explain. Such a starting point is an example of androcentrism, in that the male orgasm, which has a conceptive function and reliably occurs from genital stimulation in a sexual context, is viewed as the standard against which female orgasm is examined (Lloyd, 2005). Given that current research on orgasm indicates that genital orgasm is a specialized case of the nervous system's capacity to pleasurably release tension (Komisaruk & Rodriguez del Cerro, 2021), it does not make sense to begin with male orgasm as a starting point to understand female orgasm.

Newton's response to androcentrism was to expand what belongs to the category of female sexuality. Instead of focusing on a singular process like orgasm, Newton emphasized the interconnectedness among the entire spectrum of female reproductive processes – sex, birth, and lactation. These interconnections, via oxytocin's regulation of the female nervous system across reproductive partnerships, appear to 'lift the bounds' of female sexual pleasure. A deeper look at Newton's commitment to understanding the entirety of female reproductive biology can fruitfully guide future research into the diverse and elaborate nature of female sexual response.

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Table 5.4 Future directions for data collection and studies

Hypothesis	Predictions	Data Collection & Future Studies
'Practice for parturition'	High levels of arousal & elaborate orgasm phenotypes predict improved parturition outcomes; sexual dysfunction predicts poorer parturition outcomes.	Collect data on pre-parturition sexual function & test for correlations with labour & birth outcomes. Sexual function can be assessed using the FSFI[1], which reliably identifies sexual dysfunction, & the ESR-Q[2], which quantifies highly expressed sexual responses such as altered states & multiple orgasms. Objective birth outcomes available from birth attendants include labour duration, interventions used, & injuries sustained, & subjective birth outcomes such as emotional & pain dimensions can be obtained from parturient.
	Relationship between sexual functioning & parturition outcomes is mediated, in part, by healthy & mobile genito-pelvis.	Collect data on genito-pelvic condition, such as strength, tone, mobility, hyper-tonicity, & presence of scar tissue, with expertise of specialized physiotherapists. Test for correlations between genito-pelvic condition & sexual function, as well as genito-pelvic condition & birth outcomes.
	The capacity to surrender cognitive control predicts higher levels of arousal & elaborate orgasms, as well as improved parturition outcomes.	Psychological, self-report data assessing the capacity to surrender cognitive control using previously validated measures of absorption & creative self-forgetfulness can be tested for correlations with both sexual response & parturition data.
Cervical orgasms involve parturition mechanisms	If cervical orgasms involve mechanisms specialized for labour & birth, then vaginal birth may both impact, & be impacted by, presence of cervical orgasm.	Collect data from women prior to conception & several months postpartum (when sexual activity has resumed) on experiences of cervical stimulation, including frequency & method of stimulation, how pleasurable it is, & presence of orgasm, in addition to data on labour & birth outcomes. Test for effects of cervical pleasure &/or cervical orgasm on labour & birth outcomes, such as duration of cervical dilation. Also, assess whether women report greater enjoyment of cervical stimulation or increased likelihood of cervical orgasm following a vaginal birth. For women who delivered via planned caesarean, change in cervical pleasure or orgasm following parturition is not expected. Design a "cervical orgasm training program", with the assistance of experts that involves awareness & stimulation of the cervix for women planning to conceive. Does participation in the program increase cervical pleasure &/or cervical orgasmic capacity? Does participation in the program predict faster cervical dilation during the first stage of labour? A control training program might involve genital or perineal massage with no cervical stimulation. Safety of program would need to be assessed.

References: 1) FSFI (Female Sexual Function Index; Rosen et al 2000); 2) ESR-Q (Expanded Sexual Response Questionnaire; Ü. Sayin, *personal communication*)

5.11. References

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Chapter 6. Discussion

The minds and bodies of modern human females reveal an evolutionary history of selective pressures and adaptive compromises that shape women's capacity for pleasure as well as women's risk of pain and disorder. A deep understanding of women's health and disease requires an evolutionarily informed perspective on how the diverse demands of reproduction have woven together female psychology and physiology through shared neuroendocrine mechanisms. My above work, spread across four chapters of research, offers four main findings: (1) elevated oxytocinergic activity contributes to comorbid psychological and physiological disorder in women; (2) two of the most common reproductive disorders afflicting women involve opposite testosterone-mediated patterns of development and dysregulation of the same biological system; (3) an endometriosis diagnosis predicts positive associations between social cognition ability, pelvic pain, and depression; and (4) women's capacity for extensive sexual pleasure may involve the activation of parturition mechanisms in a sexual context and may also contribute to the optimal functioning of those mechanisms in a parturition context. These findings, particularly the first two, represent novel contributions to the fields of women's health and evolutionary medicine, and the fourth finding offers a useful re-contextualization of female sexual pleasure.

Oxytocin, a highly pleiotropic system, orchestrates diverse aspects of female physiology, psychology, and relationships, contributing to health as well as disease in women (Roney, 2016). The role of low rather than high oxytocinergic activity in disorder and disease tends to receive comparably more research attention (e.g. John & Jaeggi, 2021; Liu et al., 2022). In Chapter 2, I synthesized previously disconnected bodies of literature to demonstrate how high levels of activity in the oxytocin system contributes to uterine dysfunction, mood disorder, and the comorbidity between these physiological and psychological symptoms in women. My findings of Chapter 2 are twofold. First I confirmed evidence for comorbidity between endometriosis and bipolar disorder by comprehensively reviewing literature regarding this claim, which importantly included a new analysis of data from a study involving women with mild or subclinical bipolar features. Second, I identified, described, and evaluated the hypothesis that the oxytocin system, through its enhancing effects on uterine contractility and behavioural approach, contributes to the comorbidity between endometriosis and bipolar disorder within

women. New data is required to further investigate how oxytocin levels and/or oxytocin receptor distribution and sensitivity jointly mediates mood and uterine disorder within women, but at present, my findings represent an interdisciplinary contribution to the fields of medicine, gynecology, and psychiatry.

Findings from Chapter 2 offer practical as well as theoretical implications. Practitioners may be able to identify women at risk for endometriosis or bipolar disorder, based on the presence of one of the disorders, and treatments that target the oxytocin system, or the oxytocin-estrogen relationship, may be further explored. The relative contributions of effects from central oxytocin in the blood and peripheral oxytocin produced by the uterus will need to be better understood to apply the findings to treatments. From an evolutionary theoretical perspective, this result is interesting as it creates further questions concerning targets of selection in female psychology and physiology: could strong selection on sperm transport mechanisms drive increases in creative and extraverted cognition and behaviour via pleiotropic effects of oxytocin? To what extent is adaptive pleiotropy occurring in the female oxytocin system? How do interactions between gonadal hormones and oxytocin, and neurotransmitters and oxytocin, permit adaptive coordination of behavioural and physiological processes? The hypothesis and results in Chapter 2 exemplifies how an evolutionary medicine approach provides novel insights into mechanisms modulating patterns of disease risk.

In Chapter 3, I described and evaluated the hypothesis that endometriosis and polycystic ovary syndrome (PCOS) represent diametric disorders. This hypothesis represents a continuation of preliminary findings first described in Chapter 2, where a very small body of evidence indicated effects of reduced oxytocin in mediating uterine phenotypes characteristic of women with PCOS. Importantly, my investigation of PCOS and endometriosis as diametric disorders extended beyond oxytocin to include numerous endocrine signals, most notably testosterone, as well as other diverse phenotypes linked together by their reliance on HPG development and functioning. Through reviewing literature from endocrinology, developmental and comparative biology, morphology, physiology, and epidemiology, I demonstrated that endometriosis and PCOS involve opposite symptoms, risk factors, and correlates, apparently due to diametric alterations in the development and activity of the female HPG axis, with

disease risk modulated by opposite and extreme levels of prenatal testosterone exposure (low in endometriosis; high in PCOS).

The findings disseminated in Chapter 3 may represent the most notable contribution of my thesis work, as endometriosis - in contrast to PCOS (e.g. Corbett & Morin-Papunen, 2013) - has yet to be comprehensively investigated through an evolutionary lens. Given its high frequency and fitness reducing effects in women (Bulun et al., 2019), it represents an excellent target for such an analysis. Furthermore, the suffering of women with this condition is significant, and its burden is likely to increase due to the presence of endocrine disrupting chemicals in our environments (Rumph et al., 2020); thus, any research that might inform diagnostic, prevention, and treatment protocols is valuable. Through describing and supporting the effects of low prenatal and postnatal testosterone on HPG axis functioning, I have provided a unifying hypothesis for the risk factors, proximate causes, and symptoms of endometriosis. With further development, such contributions could potentially guide treatment protocols.

Examining endometriosis in relationship to PCOS through the diametric disorders framework also generates insights into the tradeoffs shaping female reproductive physiology and morphology. For example, to the best of my knowledge, this paper is the first to conceptualize endometriosis and PCOS as involving opposite and extreme expressions of female life history traits, such as rate of ovulation and duration of reproductive lifespan. Importantly, evidence from several animal studies demonstrated similar patterns between prenatal testosterone exposure and life history traits such as age of reproductive viability. Examining predictors of, and risk factors for, endometriosis and PCOS across socioeconomic and ethnic groups could provide further insights into contextual and environmental factors that interact with these apparent life history patterns (e.g. Wells, 2010). Additionally, the finding that endometriosis risk correlates with especially female-typical traits, such as narrow waist and low visceral fat, has already motivated another hypothesis: that endometriosis risk is maintained, in part, by sexual selection via male choice for fertility-signalling phenotypes in females (Crespi & Dinsdale, 2021). Taken together, conceptualizing endometriosis and PCOS as diametric disorders offers clinical as well as theoretical contributions.

Chapter 4 provides novel data to test predictions stemming from the first two chapters. Here, I found that, contrary to predictions, cognitive empathy skill is reduced in

women with endometriosis relative to women with PCOS and women unaffected by reproductive disorder. However, severity of pelvic pain and depression positively predicted empathy skill in women with endometriosis only, suggesting a shared endocrine basis that influences pain sensitivity, disease severity, and social cognition in affected women. The finding that severity of pain and depression positively predicts cognitive empathy ability agrees with previous research that connects sensitivity to pain with emotional insight into other people, both proximately and evolutionarily (Mischkowski et al., 2016). Indeed, pain, depression, and anxiety might motivate effort into understanding other people, particularly to discern whether other people represent potential threats or sources of social support (Harkness et al., 2005). The data described in Chapter 4 is limited due to its self-report nature and lack of measured endocrinological features. A future study might involve collecting data on hormonal levels (oxytocin, testosterone, estrogen, opioids), cognitive empathy, and current as well as chronic pain levels in women with confirmed PCOS, confirmed endometriosis, and confirmed absence of reproductive disorder. Such data would further illuminate the endocrinological bases of, and connections between, pain and empathy in women.

In Chapter 5, I shift the focus from female reproductive pain and disease to ‘normal’ or ‘healthy’ - or even ‘expansive’ - expressions of female reproductive phenotypes. I draw on research from Niles Newton and synthesize diverse literatures to evaluate three claims: first, that female sexual response is shaped and elaborated by female-specific selective pressures, such as engagement in parturition and lactation; second, that oxytocin-mediated immobility during vulnerable reproductive episodes contributes to aspects of sexual response that are particularly highly expressed in women, and third, that cervical orgasm involves the activation of labour and birth mechanisms in a sexual context.

The main contribution of this lengthy review is to encourage a shift in how we think about female sexual response, through centering a previously ignored set of evolutionary pressures that plausibly impact female sexual phenotypes. Evolutionary research into female sexual response has largely focused on how male-female mating dynamics shape the stages of desire and orgasm and comparably less attention has focused on prolonged arousal and psychological correlates of sexual response. I maintain that potential functions of female sexual phenotypes are clearer if psychological

and physiological aspects are considered as a coherent set. Instead of positing singular functions for isolated phenotypes (such as extended sexuality for resource procurement, or coital orgasm for conception with a desired mate), researchers might consider the adaptive benefits of women's capacity to experience pleasure in procreative as well as recreative contexts.

The question of why women are capable of experiencing extensive sexual pleasure through physiological and psychological pathways might inspire a greater focus on female sexual wellness rather than female sexual dysfunction. Data collection is needed to accurately characterize the full range of sexual expression available to women (e.g. Sayin, 2012). Defining the range of normal might have positive benefits on the expression of other, related reproductive processes in women, and may also illuminate the types of environments and cultures that promote female reproductive health through encouraging or permitting the full expression of female reproductive processes. Newton (1955) asserted, and supported with qualitative research, that inhibition of one sexual or reproductive process causes inhibition in others.

Overall, through the above three in-depth literature reviews and one empirical chapter, I have contributed novel insights into the proximate and ultimate causes of endometriosis and demonstrated that female-specific selective pressures must be examined if we are to comprehensively understand female sexuality. My findings can broadly be understood through the theme of extreme expression, which shapes pain and disease, as well as pleasure and wellbeing. Strong selection for a particular trait or phenotype can generate disease risk when the trait or phenotype is expressed to a very high degree, where it is more likely to become dysregulated and dysfunctional (Crespi, 2010). An example of this from my work might be strong selection on oxytocin-mediated sperm transport mechanisms contributing to endometriosis risk. Selection for increased activity of the oxytocin system in women, to meet the interpersonal, physiological, and psychological demands of female reproduction, may also engender female-elaborated and female-specific capacities, that can alter the trajectory of human culture and civilization (Hrdy, 2009).

An important issue raised throughout the above work concerns bias in research. In Chapter 2, findings indicated that elevated oxytocinergic activity has a detrimental effect on women's minds and bodies; oxytocin is generally regarded as a beneficial

hormone, which may prevent in-depth explorations of its contributions to disorder when perturbed toward relatively increased expression. Future research expanding Seng's (2013) findings, that female-preponderant mind-body disorders centrally involve high and dysregulated oxytocin release, will be useful to understand how the highly developed oxytocin system in women is particularly vulnerable to over-expression in response to traumatic life events or stress during critical periods of development. In Chapter 3, I outlined the role of low prenatal and postnatal testosterone in contributing to endometriosis. Low levels of testosterone are regularly implicated as a cause of mental and physical disorders in males (Huo et al., 2016), and high levels of testosterone are known to negatively impact female health, as evidenced in PCOS. That testosterone is generally conceptualized as a 'male' hormone may have prevented consideration of how insufficient levels of it might contribute to disorder in women. Finally, in Chapter 5, I built on Newton's (1955) and Lloyd's (2005) work to suggest that androcentric bias, as well as the related tendency to view 'sexual' processes as separate from 'reproductive' processes, has prevented evolutionary researchers from incorporating the role of female-specific selective pressures in shaping the phenotypic structure of female sexual response. Overall, these biases reveal a few different ways that labelling and describing sex-typical aspects of biology can prevent objectivity.

Females, like males, must negotiate the challenges of limited resources – time, metabolic energy, and quality mates - in the shared struggle to survive and reproduce. However, unlike males, females, as guardians of the large and finite gamete, must also negotiate the risks of receptive sexual intercourse, carry the weight of metabolically costly pregnancy, confront the emotional and physical demands of parturition and postpartum recovery, and invest significant energy into the lengthy period of lactation and child-rearing. These intimate and demanding acts of reproduction, interpersonal as well as physiological, unfold through sensitive endocrine mechanisms and developmental processes, giving rise to polarities of pleasure and pain, and patterns of health and disease, in women's lives.

6.1. References

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Appendix A.

Please answer the following questions about pain.

1) I experience pain in my pelvic region and reproductive organs

a) Never

b) Occasionally

c) Frequently

d) Constantly

2) The pain I experience in my pelvic region and reproductive organs is

a) Non-existent

b) Mild

c) Moderate

d) Severe

3) I experience pain in my pelvic region and reproductive organs, it occurs…

a)	…before my menstrual period (PMS)	never	occasionally	frequently	always
b)	…randomly throughout my cycle	never	occasionally	frequently	always
c)	…consistently throughout my menstrual cycle	never	occasionally	frequently	always
d)	…during sex	never	occasionally	frequently	always
e)	…after sex	never	occasionally	frequently	always
f)	…when I am stressed	never	occasionally	frequently	always

4) The pain I experience in my pelvic region and reproductive organs

a) does not interfere with my daily life

b) occasionally interferes with daily life

c) frequently interferes with daily life

d) almost always interferes with daily life