Let’s not forget endometriosis and infertility amid the covid-19 crisis

Introduction

Covid-19 has swamped our collective experience. It dominates the news and our lives. Hospitals are canceling surgery and people are too frightened to seek medical care. Yet the burden of disease due to infertility and endometriosis remains. Women with infertility are worried about the delay to receive services due to the cancelation of elective surgery and reduction in the availability of consultation services in many countries. Women with endometriosis face chronic pain, aggravated by higher levels of anxiety attributable to economic changes, social restrictions and fears about covid-19.

This editorial has elected to remind us that there is more to healthcare than covid-19. We have decided to refocus on the neglected needs of our patients with infertility and endometriosis, which remain important health considerations for many women. Both diagnoses are associated with psychological distress, stigma, diminished social and economic participation, and high costs to individuals and the health system. These conditions often co-exist, and women face long periods of time engaging in healthcare services to achieve their quality of life and reproductive goals.

Endometriosis

Endometriosis affects women and some in the trans-community and is a benign, chronic, estrogen-dependent, inflammatory condition, where endometrial-like mucosa spreads outside the uterus, predominantly in the pelvis. Etiology is uncertain and a definitive diagnosis requires laparoscopy. Severity of endometriosis is classified into “stages”, but although widely used, this system correlates poorly with symptom severity or reproductive prognosis [1]. Even significant endometriosis lesions may be asymptomatic. Therefore, prevalence estimates are imprecise but, in high-income countries, range from 1 to 2% in populations of women of reproductive age. It is a common gynecological presentation (6–10% in clinical samples) but is often only diagnosed during investigations for infertility [2]. Less is known about endometriosis in low-income settings. Treatment options in primary care are limited to analgesics and hormonal suppression of ovarian function, which may be associated with side effects. Lesions removed surgically commonly recur [2], although ongoing medical suppression can prevent or reduce recurrence. Women may engage with multiple healthcare providers in the pursuit of symptom relief.

Link to infertility

Some women with endometriosis experience infertility or sub-fertility. Population-based studies suggest women with self-reported symptoms consistent with endometriosis are three times more likely to report an infertility diagnosis and six times more likely to report taking longer than 12 months to conceive [3]. The prevalence of endometriosis is nearly 10-fold higher in women experiencing infertility than in the general population, suggesting a causal relationship in some cases [4]. However, prevalence estimates of endometriosis among women experiencing infertility derived from cross-sectional data are likely to be inflated because otherwise asymptomatic endometriosis may be an incidental finding of infertility investigations. Further, hormonal and surgical treatment of endometriosis lesions may not improve fertility [1].

Confirmation of causality requires that endometriosis precede infertility. One landmark study by Prescott and colleagues prospectively investigated timelines using data from a sample of married women under 40 years of age (n = 58,427) from the US Nurses’ Health Study II. A history of laparoscopically confirmed endometriosis was associated with twice the likelihood of subsequent infertility from any cause (age-adjusted hazard ratio; 95% CI = 2.12; 1.76–2.56 p<.0001). The precise potential biological mechanisms underlying the association, especially any differences between symptomatic and asymptomatic endometriosis, remain poorly characterized [4].

The increasing use of assisted reproductive technologies (ART) in recent years has focused research interest on pregnancy outcomes in the context of endometriosis. A recent systematic review and meta-analysis [5] of 33 observational studies compared outcomes between participants with and without surgically diagnosed endometriosis. Pooled results (n = 3,289,488 participants) showed significantly higher odds of many pregnancy complications including preeclampsia, hypertension and/or pre-eclampsia, gestational diabetes, gestational cholestasis, postpartum hemorrhage, antepartum hemorrhage birth complications and cesarean section. Significantly, higher odds of adverse fetal and neonatal outcomes were also documented including premature rupture of membranes, pre-term birth, small for gestational age, admission to NICU, stillbirth and neonatal death. Where comparison of outcomes is possible, these findings were broadly consistent with an earlier systematic review of 24 studies involving 1,924,114 participants [6]. Because there is likely to be higher prevalence of endometriosis among women
conceiving with ART, use of ART is a potential confounder. Lalani and colleagues, therefore, compared pregnancy outcomes among women who conceived spontaneously and with ART. The findings were consistent except for cesarean section and low birth weight, suggesting that endometriosis is an independent risk.

Despite evidence of reduced fertility and higher probability of pregnancy complications, women with endometriosis are often advised by healthcare providers that pregnancy would reduce their endometriosis symptoms and disease progression [7]. This advice is based on observations of cyclic changes, including luteal phase transformation of endometrial lesions, throughout the menstrual cycle. It is, therefore, thought that the high progesterone milieu during pregnancy supports regression of endometrial lesions. However, the evidence about regression of lesions or reduction of symptoms, such as pain during or after pregnancy is inconsistent and does not support a beneficial effect of pregnancy except for dysmenorrhea [8].

**Emotional cost**

Endometriosis can be physically and emotionally debilitating. In a multi-center study [9], 1486 women scheduled for laparoscopy in 10 countries completed a 67-item self-report questionnaire in their own language. The results confirm that endometriosis has serious adverse consequences for women’s health, quality of life and economic participation. Adjusting for relevant covariates (education, marital status, employment status, pelvic pain severity, type and number of presenting symptoms and comorbidity), compared with women in the study who reported similar symptoms but no endometriosis (n = 587), women subsequently diagnosed with endometriosis (n = 745) in all participating countries reported significantly lower health-related quality of life in physical functioning (p = .02), physical (p = .013) and mental (p = .022) role limitation and bodily pain (p = .039). Endometriosis was associated with significantly worse absenteeism (p = .019), presenteeism (p = .033) and increased overall work productivity loss (p = .014). Financial costs of endometriosis to individual women were high in all participating countries. The mean interval between first presenting with symptoms to primary care and definitive diagnosis of endometriosis was almost 7 years and associated with an average seven visits before referral to a gynecologist [9], confirming high costs to the health system as well.

**A contested disease**

Endometriosis can be difficult to diagnose clinically. Presentations are varied and include heavy menstrual bleeding, pelvic pain especially with menstruation, fatigue, bowel and bladder comorbidities, psychological distress, pain during sexual intercourse, and infertility. Work-up in primary care can be time consuming because of the need to exclude other potential causes [10]. Much scholarly effort has been devoted to investigating the drivers of the endometriosis “diagnostic delay”. Drawing on sociological theory, Denny and Weckesser describe endometriosis as a “contested disease” because there is “no general consensus about the nature of its cause, its progression and treatment, or indeed whether it exists at all”. These features are exacerbated in endometriosis because a degree of dysmenorrhea is universal, and by social concealment of menstruation resulting in a lack of disclosure and discussion of intimate symptoms not visible to others. This leads to uncertainty among women, their families and health professionals about the boundary between normal and abnormal menstruation. Women’s symptoms are frequently trivialized or disbeliefed, consequently attributing pathology to the woman rather than the disease, which is deeply distressing [11]. These responses are underpinned by essentialist notions that pain is just part of being a woman. Lack of legitimation results in victim blaming, reinforces gendered stereotypes about feminine weakness, intensifies women’s distress and averts prompt action [10].

Similar essentialist ideas underlie observations that framing endometriosis as a fertility problem is more likely to result in health care intervention than when it is framed as symptom management. In one qualitative study, women described fertility as the entry point for discussion about endometriosis, despite having sought health care for symptoms over many years [12]. Existing evidence about best practice fertility-related care for women with endometriosis is sparse. However, conflicting advice and treatment options, such as fertility testing (AMH and tubal patency) ovulation stimulation, oocyte retrieval and freezing, donor sperm, intrauterine insemination and IVF may be offered to women without acknowledgment of medical uncertainty, confirmation that a woman’s fertility is actually compromised or that she desires or her social circumstances support her willingness to conceive. Participants reported satisfaction with care that involved sensitive inquiry and listening, and advice that acknowledges their sexuality and reproductive goals and that addresses their specific concerns with available evidence-based information [12]. Dyspareunia is a common and distressing symptom of endometriosis, and intimate relationships and sexuality are central concerns of couples experiencing infertility [13] argue that multi-disciplinary care should include sexology to address couples’ psychosexual needs and promote wellbeing.

Treatment of endometriosis and infertility prompt complex clinical questions without simple answers. Together, the two conditions have important global research, health care and policy implications. In the midst of a global focus on covid-19, it remains important to realize that for many women life goes on and the burden of chronic disease still needs to be managed, even if
resources are being diverted to other areas. We can still offer symptom control and counseling to help women navigate this difficult time.

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