J Epidemiol Community Health. Author manuscript; available in PMC 2022 April 27.

The Epidemiology of Gynecologic Health: Contemporary Opportunities and Challenges

Sarah R. Hoffman, MS, MPH[1], **Leslie V. Farland, ScD**[2], **Kemi M. Doll, MD, MSCR**[3], **Wanda K. Nicholson, MD, MPH, MBA**[4,5,6], **Maya A. Wright, MPH**[1], **Whitney R. Robinson, PhD, MSPH**[1,7]

[1]Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC, USA

[2]Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

[3]Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA, USA

[4]Department of Obstetrics and Gynecology, UNC School of Medicine, Chapel Hill, NC, USA

[5]Center for Women's Health Research, University of North Carolina, Chapel Hill, NC, USA

[6]Center for Health Promotion and Disease Prevention, University of North Carolina, Chapel Hill, NC, USA

[7]Carolina Population Center, University of North Carolina at Chapel Hill, NC, USA

Abstract

Non-cancerous gynecologic conditions have long been neglected in epidemiologic research. The field of reproductive epidemiology has primarily focused on reproduction and life-threatening gynecologic cancers, thereby marginalizing the suffering associated with non-malignant gynecologic conditions. This narrow focus downplays the common and life-altering impacts that non-malignant gynecologic conditions have on quality of life, economic well-being, as well as physiologic, psychosocial and sexual health. We argue that women's bodies should be studied for their own sakes and not just for their reproductive function. Then we identify and illustrate three critical research complexities to address to advance the epidemiology of non-malignant gynecologic conditions. With greater investment and a patient-centered approach, epidemiology can advance knowledge about this critical area of health.

Condensation

Epidemiology has neglected gynecologic conditions that do not involve pregnancy, childbirth, or cancer. To advance the epidemiology of non-malignant gynecology, we recommend three methodological issues to prioritize.

Corresponding Author: Whitney R. Robinson, PhD, MSPH Department of Epidemiology CB# 7435, Chapel Hill, NC 27599-7435.

Competing Interest: None declared.

Keywords

gynecology; reproductive health; epidemiological methods; clinical epidemiology; gender

Introduction

In this commentary, we argue that the epidemiology of non-malignant gynecologic conditions is under-resourced. Non-malignant gynecologic conditions of the vagina, uterus, and ovaries are deleterious to physical health and the sufferer's quality of life. These non-cancerous conditions include uterine fibroids, abnormal uterine bleeding, endometriosis, adenomyosis, adnexal masses, pelvic inflammatory disease, polycystic ovarian syndrome (PCOS), and vulvar pain conditions, among other conditions [1][2], Non-malignant gynecologic conditions diminish psychosocial health, increase psychologic distress, impair sexual function, and harm economic well-being by, for instance, increasing days missed from work.[3]

We argue that there is relatively little investment in the epidemiology of non-malignant gynecologic conditions because most societies devalue the pain, time, and well-being of women.[4,5] For instance, when it comes to the limited pool of resources devoted to reproductive epidemiology, the field has prioritized topics related to birth and death: on the birth side, the ability to conceive and birth children;[6] on the death side, life-threatening gynecological cancers, such as ovarian or endometrial cancer.[4] This focus neglects the high prevalence of non-cancerous gynecological diseases that impair quality of life for many non-pregnant cis-gendered women, trans-gendered men, and non-binary people; those not trying to conceive; and many post-reproductive-aged cis-gendered women. For instance, a gynecologically related condition like anemia places a huge burden on women in both wealthy nations and low and middle income ones. [7]

The Reproductive Epidemiology chapter of the *Handbook of Epidemiology* illustrates the shunting of non-reproductive-related gynecologic issues to other fields:

"Many diseases of the reproductive organs, like cancer or infections, may have an effect on reproduction if the diseases appear before or during reproductive age. In most cases, studying the determinants of these diseases will be similar to studying determinants of other diseases and, as such, they are not pertinent to the analysis in this chapter."[8]

Indeed, gynecologic cancers and infections may find disciplinary homes in cancer and infectious disease epidemiology. But where does such a narrow focus of reproductive epidemiology leave the epidemiology of non-malignant gynecologic conditions? The neglect of the epidemiology of non-malignant gynecologic conditions leaves these conditions without the funding and research infrastructure to advance knowledge about their etiology, prevention, and treatment.

In the United States, funding for gynecologic conditions has been disproportionately low. For instance, the National Institutes of Health (NIH) is expected to award endometriosis, uterine fibroid, and vulvodynia research $12 million, $16 million, and $2 million, respectively, in fiscal year 2021.[9] In comparison, for this same time period, chronic obstructive pulmonary disease, which affects 6.2% of the U.S. population, is expected to receive $107 million; Crohn's disease, which affects <1% of the population, will receive $74 million; and inflammatory bowel disease will receive $158 million.[9] A recent NIH study supports the contention that gynecologic conditions, and the larger field of women's reproductive health, is under-resourced. The study identified 150 topical clusters funded by the NIH in 2011–2015. The cluster with the absolute lowest likelihood of funding was the one characterized "by the [gendered] words 'ovary,' 'fertility,' and 'reproductive'.[10] This area's funding likelihood was 7.5%, compared to 28.7% for the cluster most likely to be funded. This funding discrepancy shows that even reproduction-focused reproductive health is underfunded in the U.S. A sub-field like gynecologic health is even less likely to receive funding. Globally, there is also limited funding dedicated to gynecologic research in other high-income countries [11] [12], And there is anecdotal evidence that, in many low and middle-income countries (LMICs), there is little dedicated funding at all [13].

While there are productive and dedicated researchers who work in gynecologic epidemiology, they often do so with limited resources. The only NIH entity to focus on this area, the Gynecologic Health and Disease Branch (GHDB), was established less than 10 years ago and has a small budget relative to the burden of gynecologic conditions.[14] As a result, there are few institutions today with centers focused on non-malignant gynecologic epidemiology.[15] Moreover, many of the limited training programs, like the NIH's "Women's reproductive Health Research Career Development Program," are exclusively for physician-scientists and exclude PhD-trained epidemiologists.

Besides the discounting of the well-being of women, gynecologic epidemiology may be under-resourced because there is a perception that its issues are not urgent. One might ask, "Why study diseases that are not fatal and can be treated?" While there are treatment options for these conditions, many of these treatments either fail overtime, are invasive, require long-term medication use, or are incompatible with people's desires for fertility. Moreover, the eventual remission of symptoms after decades of suffering does not remove the onus from the public health community to prevent these conditions and provide effective, non-invasive, long-term treatments that are compatible with people's possible desires for fertility and to avoid long-term medication use.

In this commentary, we argue that the epidemiology of gynecologic health is characterized by a unique set of methodologic complexities that warrant further attention. By devoting resources to address these methodological challenges, the field of gynecologic epidemiology can accelerate the growth of knowledge. Further, the development of richer data infrastructure, epidemiologic methods, and expertise will have positive spillover effects for other fields. Below we describe three key methodologic complexities salient to gynecologic epidemiology.

Methodologic complexities to address to catalyze the advance of epidemiologic studies of non-malignant gynecologic disorders

Missing Cases

Difficulty in identifying cases is a major challenge of research studies of gynecologic conditions. Non-malignant gynecologic conditions are often subclinical. When symptoms of gynecologic conditions like uterine fibroids or endometriosis develop, they are often self-managed. For instance, heavy menstrual bleeding and pain may not be discussed with a health care provider because a woman considers it “normal.”[16–18]. This self-management may be especially common if the disease runs in the family and is normalized within the familial and community networks. The sociocultural context may also impart a stigma that affects patients’ reports of their own symptoms. Even if patients are in contact with the healthcare system, stigma and embarrassment about discussing menstruation and sex with health care providers may impair a person’s ability to articulate symptoms.[12] Moreover, even when patients do complain of gynecologic pain or symptoms, providers may minimize or deny these complaints (“medical gaslighting”) .[19], causing the patient to doubt his or her own perceptions and minimize symptoms. For example, it is estimated that globally, on average, there is a seven year delay between symptom onset and diagnosis for women with endometriosis.[19] Additionally, anomalies such as decidual casts (i.e., shedding of the uterine lining in one piece, in the shape of the uterine cavity)[20] or galactorrhea (e.g., spontaneous lactation)[21] may manifest as transient episodes that may resolve before the person seeks treatment, rendering their measurement and study difficult.

Moreover, many women may not receive a diagnosis because of limited access to appropriate health care. Financial, geographic, or time constraints can all restrict health care access. These barriers access are present in many countries but may be especially common in LMICs.

Finally, these barriers to diagnosis within clinical settings affect epidemiologic research conducted outside of clinical settings. Because gynecologic conditions are underdiagnosed and frequently dismissed by authority figures, they may not be identified with high sensitivity by self-reports. All the factors described above lead to disease under-ascertainment in gynecologic epidemiology research. Without addressing this under-ascertainment, the field can be hampered by biases such as outcome misclassification bias and selection bias.

Clinical Case Definitions

Another barrier facing gynecologic epidemiology is the clinical challenge of differential diagnosis. This challenge manifests as outcome misclassification in epidemiologic studies. The incidence and prevalence of gynecologic conditions will remain challenging to study as long as diagnostic tests are non-specific, relatively invasive, and expensive. For example, a woman may present with primary dysmenorrhea and heavy menstrual bleeding. However, these are symptoms of a number of gynecologic conditions including uterine fibroids, endometriosis, and adenomyosis. Further, many gynecologic conditions share symptoms with non-gynecologic conditions, such as abdominal pain, which is a symptom of irritable bowel syndrome, Crohn's disease, and some cancers.

Currently, definitive diagnoses of many gynecologic conditions require invasive surgical procedures. For example, diagnosing endometriosis involves laparoscopy, a surgical procedure in which endometriosis is visualized and often removed for pathological examination.[22] Thus, diagnosing endometriosis requires a patient's time, logistical ability, and sufficient health status to undergo a potentially expensive surgical procedure under anesthesia that may not even result in a definitive diagnosis. Diagnosis of adenomyosis relies on an even more invasive surgery: hysterectomy and pathology of the uterine tissue.[22] While imaging methods like MRI and transvaginal ultrasound are emerging as alternative diagnostic methods, these techniques provide less definitive and sensitive detection of adenomyosis than a pathology report after hysterectomy.[23] One example of how difficulty in diagnosis can effect gynecologic epidemiology is the relationship between childbearing and adenomyosis. Because diagnosis for this disease relies on hysterectomy, adenomyosis is more likely to be diagnosed in women who have already completed childbearing. As a result, a relationship between parity and adenomyosis may be biased by disproportionately greater likelihood of definitive diagnosis among parous versus nulliparous patients. Lack of sensitive and specific diagnostic criteria that are relatively non-invasive complicates research on the descriptive (e.g., incidence) and mechanistic epidemiology of many gynecologic conditions.[23,24]

On the other extreme, incidental diagnosis of non-symptomatic gynecologic conditions is common and may lead to etiologically heterogenous categories of gynecologic conditions. For example, an incidentally diagnosed case of endometriosis during a work-up for infertility may be etiologically and phenotypically distinct from symptomatic cases of endometriosis that present with pain.[25] Patients detected during an infertility evaluation recognized their difficulty conceiving and had access to infertility care, which is expensive and relatively inaccessible in many parts of the world.[26] Therefore, studying a case series in which these incidentally detected cases are overrepresented may result in spurious associations with socioeconomic status, health literacy, and access to care. The potential for spurious associations with factors that predict greater likelihood of incidental diagnosis instead reflecting true underlying incidence reinforces the need for population-based studies of gynecologic conditions and attention to case definitions and diagnosis modes.

Finally, we acknowledge that the needs of clinical practice and epidemiologic research differ when it comes to case definitions for non-malignant gynecologic conditions. In accordance with the American College of Obstetrics & Gynecology (ACOG) guidelines, many providers will presumptively diagnose conditions based upon symptoms alone. The alternative is subjecting patients to expensive and invasive diagnostic procedures whose results might not change providers' treatment recommendations.[22] For some mild to moderate cases, medications such as hormonal contraceptives may be used to reduce pain and bleeding even in the absence of diagnosis.[3,27] Forgoing definitive diagnosis is an optimal decision for many patients. However, lack of specific, non-invasive case definitions prevents epidemiologists from identifying phenotypically homogenous, population-based samples of those with disease. Population-based samples would enable epidemiology to conduct high-quality etiologic research to calculate incidence of each condition and identify causes of these conditions.

Measuring and analyzing dynamic exposures, outcomes, and covariates

The final complexity of the epidemiology of gynecologic conditions is the measurement and analysis of key time-varying variables. One salient issue if the cyclical nature of the menstrual cycle. For instance, gonadal and hypothalamic hormones, which are important in research on gynecologic conditions, vary over the menstrual cycle. Even non-hormones, such as iron are known to vary across the menstrual cycle. In gynecologic-related etiologic research involving biomarkers, blood must be drawn at a consistent time in the menstrual cycle in order for the lab values to be comparable, whether within or between women.[25] However, collecting high-quality, comparable, data is not as simple as asking women to present for blood collection on the n^{th} day of their cycles, because not all cycles are the same length and not all people are willing to track their cycles. This issue interacts with the social stigma against menstruation and female reproductive body parts. This stigma may cause some people to avoid paying attention to their own cycles and bodies out of shame or disgust. Similarly, use of health care data is often not a feasible solution: clinicians are unlikely to obtain laboratory values on the same day of the menstrual cycle for most patients. The dynamic nature of gynecologic systems requires specialized expertise in data collection and advanced approaches to data analysis.

In addition to the cyclical nature of key biological variables in gynecologic epidemiology, many other key covariates (e.g., pregnancy, lactation, and hormonal contraceptive use) difficult to measure or vary over time. For example, hormonal contraceptives are an important potential mediator, effect modifier, and confounder in many studies of gynecologic health. However, recall is challenging,[28] given that women report using a median of five hormonal contraceptive types across their lifetimes.[29]

Other key covariates are not routinely captured. For instance, a person’s desire to maintain the possibility of future fertility is missing from many studies. This time-varying preference is a strong determinant of type of gynecologic health care chosen. Unfortunately, it is not uniformly reported in claims data or electronic health records nor always measured by cohort studies. Moreover, social correlates of gynecologic health and health care such as race/ethnicity, individual-level socioeconomic status, stress pathways, and aspects of place and health care systems are often unmeasured in gynecologic epidemiology studies. Finally, as noted throughout this paper, the sociocultural context in which people experience their menstrual cycles (or lack thereof) and organs of the gynecologic system affects observation of and communication about gynecologic health. Sociocultural contexts remain deeply influential but largely unmeasured forces in gynecologic epidemiology.

Conclusion and recommendations for researchers

Reproductive health, as defined by the World Health Organization, concerns the reproductive system at all stages of life.[30] Unfortunately, the emphasis of reproductive epidemiology as a field has been on reproductive *capacity* and *function,* rather than on the health of the reproductive system and its effects on quality of life across the life course.[4,8]

The totality of reproductive health will remain obscured if critical research challenges in gynecologic health are not addressed. The methodologic complexities described above - difficulty identifying people with subclinical disease; the need for more sensitive and specific case definitions that can be applied in population-based research; and measurement of key variables - are challenging but can be overcome. Knowledge about the population-level epidemiology of gynecologic health can advance if biomedical funding invests in validating self-report measures of gynecologic conditions; developing accurate, scalable case definitions that do not rely on invasive or expensive medical procedures; nuanced, high quality data collection incorporating the cyclical and time-varying nature of key variables; and the incorporation of study designs and data analysis techniques that can address missing data and time-varying variables and identify mediation and modification.

We urge a patient-centered approach in all gynecologic research. Women's and transgender and non-binary people's bodies have long been heavily politicized. [4,5] Further, gynecologic conditions and their treatments may have long-term consequences for self-concept, sense of agency, and achievement of life goals. Interactions around gynecologic health often implicate and complicate personal identity more than treatment for other conditions. When health researchers design their research in a patient-centered manner, not only are the causal inferences stronger, but the work will be more valuable for the end users of the research.

In conclusion, we have argued that more resources and research should be focused on gynecologic epidemiology. Non-malignant gynecologic conditions affect tens of millions of people and can severely impact quality of life. Therefore, a well-funded, methodologically rigorous, and person-centered gynecologic epidemiology has the potential to improve the health and well-being of tens of millions. Gynecologic epidemiology is a field that has made remarkable strides with relatively low levels of sustained investment. With more resources to understand these conditions and tackle these methodological complexities, the field can be a scientific leader and improve the health and wellbeing for people around the world.

References

1. Boyle and Torrealday - 2008 - Benign Gynecologic Conditions.pdf. https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S003961090700179X.pdf?locale=en_US&searchIndex= (accessed 25 Oct 2019).
2. Bachmann GA, Rosen R, Pinn VW, et al. Vulvodynia: a state-of-the-art consensus on definitions, diagnosis and management. J Reprod Med 2006;51:447–56. [PubMed: 16846081]
3. Jones GL, Kennedy SH, Jenkinson C. Health-related quality of life measurement in women with common benign gynecologic conditions: A systematic review. Am J Obstet Gynecol 2002; 187:501–11. doi: 10.1067/mob.2002.124940 [PubMed: 12193950]
4. Inhorn MC, Whittle KL. Feminism meets the "new" epidemiologies: toward an appraisal of antifeminist biases in epidemiological research on women's health. Soc Sci Med 2001;53:553–67. doi:10.1016/S0277-9536(00)00360-9 [PubMed: 11478536]
5. Germain A The global movement for sexual and reproductive health and rights: Intellectual underpinnings. In: Global Health and Security: Critical Feminist Perspectives. Routledge 2018. 78–95.
6. Mayne SL, Pool LR, Grobman WA, et al. Associations of neighbourhood crime with adverse pregnancy outcomes among women in Chicago: analysis of electronic health records from 2009 to

2013. J Epidemiol Community Health 2018;72:230–6. doi: 10.1136/jech-2017-209801 [PubMed: 29305526]

7. Harris-Fry HA, Azad K, Younes L, et al. Formative evaluation of a participatory women's group intervention to improve reproductive and women's health outcomes in rural Bangladesh: a controlled before and after study. J Epidemiol Community Health 2016;70:663–70. doi: 10.1136/jech-2015-205855 [PubMed: 26739272]
8. Ahrens and Pigeot - 2005 - Handbook of epidemiology with 180 tables.pdf. 10.1007/978-3-540-26577-1.pdf (accessed 2 Feb 2020).
9. NIH Categorical Spending -NIH Research Portfolio Online Reporting Tools (RePORT). https://report.nih.gov/categorical_spending.aspx (accessed 12 Feb 2020).
10. Hoppe TA, Litovitz A, Willis KA, et al. Topic choice contributes to the lower rate of NIH awards to African-American/black scientists. Sci Adv 2019;5:eaaw7238. doi: 10.1126/sciadv.aaw7238 [PubMed: 31633016]
11. Norges forskningsråd. https://www.forskningsradet.no/ (accessed 25 Oct 2019).
12. Serour GI. Global Work of the International Federation of Gynecology and Obstetrics (FIGO). Facts Views Vis ObGyn 2012;4:3–8.
13. Robinson Whitney R. (@WhitneyEpi), et al. Ok, non-U.S. #epitwitter, I need info for a commentary I'm writing. How is population-based gynecologic research (e.g., #endo, #fibroids, #PCOS) funded in your country? 1/n.2019.https://twitter.com/WhitneyEpi/status/1180214195943563267?s=20 (accessed 16 Feb 2020).
14. Gynecologic Health and Disease Research at NICHD. https://www.nichd.nih.gov/sites/default/files/2018-06/GHDB_ScientificVision_2018.pdf (accessed 25 Oct 2019).
15. Women's Reproductive Health Research (WRHR) Career Development Program. https://www.nichd.nih.gov/.https://www.nichd.nih.gov/research/supported/wrhr (accessed 22 Jul 2020).
16. Ghant MS, Sengoba KS, Vogelzang R, et al. An Altered Perception of Normal: Understanding Causes for Treatment Delay in Women with Symptomatic Uterine Fibroids. J Womens Health 2016;25:846–52. doi:10.1089/jwh.2015.5531
17. Chibber S, Mendoza G, Cohen L, et al. Racial and ethnic differences in uterine fibroid prevalence in a diverse cohort of young asymptomatic women (18–30 yo). Fertil Steril 2016;106:e97. doi: 10.1016/j.fertnstert.2016.07.281
18. Sengoba KS, Ghant MS, Okeigwe I, et al. Racial/Ethnic Differences in Women's Experiences with Symptomatic Uterine Fibroids: a Qualitative Assessment. J Racial Ethn Health Disparities 2017;4:178–83. doi:10.1007/s40615-016-0216-1 [PubMed: 27068661]
19. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011 ;96:366–373.e8. doi: 10.1016/j.fertnstert.2011.05.090 [PubMed: 21718982]
20. Brandão P, Portela-Carvalho A, Oliveira C. Non-Painful Out of Pill Membranous Dysmenorrhoea. Obstet Gynaecol Cases - Rev 2018;5. doi:10.23937/2377-9004/1410137
21. Leung AKC, Pacaud D. Diagnosis and Management of Galactorrhea. Am Fam Physician 2004;70:543–50. [PubMed: 15317441]
22. Boyle KJ, Torrealday S. Benign Gynecologic Conditions. Surg Clin North Am 2008;88:245–64. doi:10.1016/j.suc.2007.12.001 [PubMed: 18381112]
23. Abbott JA. Adenomyosis and Abnormal Uterine Bleeding (AUB-A)—Pathogenesis, diagnosis, and management. Best Pract Res Clin Obstet Gynaecol 2017;40:68–81. doi:10.1016/j.bpobgyn.2016.09.006 [PubMed: 27810281]
24. Giudice Linda C., Kao Lee C. Endometriosis. The Lancet 2004;364:1789–99. doi: 10.1016/S0140-6736(04)17403-5
25. Shafrir AL, Farland LV, Shah DK, et al. Risk for and consequences of endometriosis: A critical epidemiologic review. Best Pract Res Clin Obstet Gynaecol 2018;51:1–15. doi:10.1016/j.bpobgyn.2018.06.001 [PubMed: 30017581]
26. Farland LV, Collier AY, Correia KF, et al. Who receives a medical evaluation for infertility in the United States? Fertil Steril 2016;105:1274–80. doi:10.1016/j.fertnstert.2015.12.132 [PubMed: 26785253]

27. Durain D Primary Dysmenorrhea: Assessment and Management Update. J Midwifery Womens Health 2004;49:520–8. doi:10.1016/j.jmwh.2004.08.013 [PubMed: 15544981]
28. Louis GMB, Hediger ML, Peterson CM, et al.. Incidence of endometriosis by study population and diagnostic method: the ENDO study. - Abstract - Europe PMC. Fertil Steril 2011;96:360–5. doi:10.1016/j.fertnstert.2011.05.087 [PubMed: 21719000]
29. Daniels K, Mosher WD. Contraceptive methods women have ever used: United States, 1982–2010. Natl Health Stat Rep 2013;: 1–15.
30. Preventing Reproductive Health Problems. https://www.who.int/ceh/capacity/preventing_reproductive_problems.pdf?ua=1 (accessed 25 Oct 2019).