SCOPING REVIEW OF LEVONORGESTREL PHARMACOKINETIC DATA IN SPECIAL POPULATIONS

KEY TAKEAWAYS

KEY TAKEAWAY 1: There is a scarcity of levonorgestrel (LNG) pharmacokinetic data for multiple special populations. This highlights an abundant opportunity to learn more about potential pharmacokinetic changes in special populations with altered physiology that may plausibly impact absorption, distribution, metabolism, and excretion (ADME) processes.

KEY TAKEAWAY 2: Current data suggests potentially different pharmacokinetic profiles of LNG among undernourished populations and those with gastrointestinal illnesses. However, additional investigation is needed for these conditions along with other prevalent conditions in low- and middle-income countries (LMICs) that may affect ADME processes.

KEY TAKEAWAY 3: Due to insufficient data and methodological limitations, LNG physiologically based pharmacokinetic (PBPK) models may be less precise for particularly vulnerable populations in LMICs where different and overlapping disease burdens may impact LNG efficacy.

BACKGROUND

Levonorgestrel (LNG) is a widely used hormonal contraceptive with both emergency and non-emergency use applications. Its formulations include oral pills, long-acting methods such as intrauterine devices (IUDs) and subdermal implants, and emerging technologies like microneedle patches and hydrogels. Each route of administration has a distinct pharmacokinetic (PK) profile, which influences drug absorption, distribution, metabolism, and excretion (ADME) (Appendix 1). Long-acting LNG formulations are particularly relevant in low-and middle-income countries (LMICs), where they provide reliable options to prevent unintended pregnancies, along with other benefits including reduced menstrual bleeding and dysmenorrhea[1]. However, ensuring their safety and efficacy requires understanding how the drug behaves in diverse populations, particularly those with health conditions that could alter PK processes.

Existing literature on LNG PK appears to focus on a narrow range of participants, lacking diversity in terms of age, health, and ethnicity, with the most recent multi-route review published in 1995 (Fotherby)[2]. Contraceptive practice recommendations for the United States (U.S.) highlight a lack of evidence for women experiencing gastrointestinal illnesses while taking oral contraceptives. Recommendations are based on missed pill protocols rather than actual PK data assessing the effects of vomiting/diarrhea on absorption. Additionally, guidelines stipulate that screening for conditions such as liver disease are not conducted due to their low prevalence in the U.S.[3]. These recommendations and lack of diverse study populations could be an issue for special population groups as PK profiles may vary substantially. For example, Fotherby concluded that a study reporting vastly different half-lives for distribution and elimination among Indian women must be erroneous despite the participants having an altered nutritional status, which suggests that our current data may not fully capture how LNG behaves across different groups[4]. In women with a body mass index above 30 kg/m^2 LNG is considered less effective, but its efficacy in populations with different health conditions is not as clear[3].

Pathologies such as liver disease, undernutrition, and diarrheal diseases are more common in LMICs than in higher income settings where PK studies are typically conducted and may significantly impact LNG pharmacokinetics[5,6,7]. For example, liver enzymes play a key role in LNG metabolism and impaired hepatic function may alter drug metabolism and corresponding efficacy. Similarly, undernutrition and diarrheal diseases can affect drug absorption, distribution, and metabolism. Physiological changes such as decreased lean body mass and impaired hepatic function are well-documented contributors to PK alterations[8]. Additionally, specific conditions such as female genital schistosomiasis (FGS), which affects 16–56 million women globally, may also influence LNG PK by altering drug distribution and metabolism from associated liver disease and scarring of genital tissues[9]. Recognizing these interactions is crucial for improving contraceptive care, optimizing dosing recommendations, and promoting global health equity.

This scoping review aims to map the existing literature on LNG pharmacokinetics across different formulations and in special population groups, namely those with liver disease, undernutrition, female reproductive tract abnormalities, and gastrointestinal illnesses (GI).

METHODS

Peer-Reviewed Literature

We searched three databases (PubMed, Embase, and Global Index Medicus) for articles containing LNG PK data in populations with pathophysiology theorized to impact LNG ADME, published globally up to November 18, 2024 (Appendices 1 & 2).

Covidence was used to manage search results and screen articles for eligibility based on inclusion and exclusion criteria (Table 1).

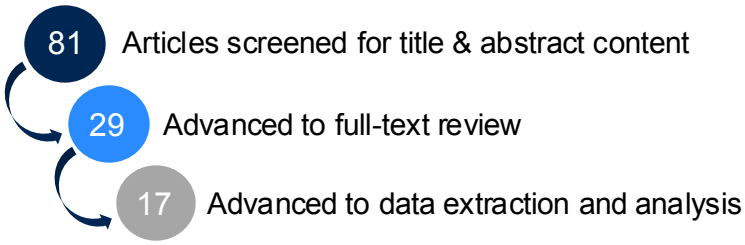


Table 1: Scoping Review Inclusion and Exclusion Criteria for Peer-Reviewed Literature

Inclusion Criteria	Exclusion Criteria
Levonorgestrel PK data in humans or animals	No PK data
Any pathophysiology that might impact LNG PK	Only healthy populations
Any route of administration	Emergency contraception
Any geography	Non-hormonal contraception
Any age	Protocols
Any study design	

Information on article metadata, study design, special populations of interest, LNG dosing, PK parameters, key findings, and other relevant information were extracted into an Excel spreadsheet. For ease of reference screenshots of relevant figures/tables with PK data from each empirical study were compiled into a Word document.

Sources of PK Data from Regulatory Agencies

We explored the websites of six drug regulatory agencies: United States Food and Drug Administration (FDA); European Medicines Agency (EMA); Pharmaceuticals and Medical Devices Agency (PMDA) of Japan; South African Health Products Regulatory Authority (SAHPRA); Therapeutic Goods Administration of Australia; and Health Canada. Of these sources, the FDA had the most publicly available PK data for LNG therapies, so we focused our review on this agency's database.

We searched the Drugs@FDA database for FDA-approved LNG products and reviewed all 11 non-oral therapies for PK data in special populations due to their relevance for LMIC settings[10]. We gave particular attention to available Pharmacology Reviews and Clinical Pharmacology Biopharmaceutics Reviews, which typically contain the most comprehensive PK data for each product.

DESCRIPTIVE RESULTS

Sources of PK Data from Regulatory Agencies

Non-oral LNG formulations in the FDA database did not include any special populations with abnormal pathophysiology that would be expected to impact LNG ADME properties. However, they sometimes included healthy women, women with higher Body Mass Index (BMI), post-menopausal women, or adolescents.

Peer-Reviewed Literature

The 17 identified articles covered seven special populations with altered physiology that could potentially impact LNG PK: six articles on undernutrition, five articles on gastrointestinal (GI) illnesses, and one article each on cystic fibrosis, liver disease, schistosomiasis, uterine fibroids, lung disease, and B-cell malignancies (Figure 1).

All but three articles were published between 1979 and 1990, demonstrating the lack of published research on this topic in recent decades. Of the three newer articles, two are drug-drug interaction (DDI) studies with no healthy population controls for comparison of levonorgestrel PK data. The third is a systematic review on contraceptive use in women with inflammatory bowel disease.

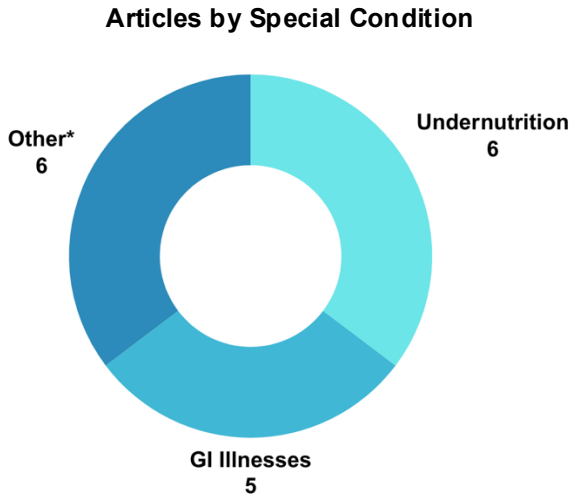


Figure 1: Number of articles found for each special population

*Other: cystic fibrosis, liver disease, uterine fibroids, schistosomiasis, lung disease, and B cell malignancies

Fifteen articles are empirical studies. Four studies contain *in vivo* LNG PK data in animals, while the remaining 11 non-review articles report human clinical data. Reported LNG PK parameters varied by study, but covered plasma or tissue concentrations, including maximum (C_{max}) and minimum (C_{min}) concentrations; bioavailability; area under the curve (AUC); time to maximum concentration (T_{max}); half-life ($t_{1/2}$); and volume of distribution (Vd).

TABLE 2: DESCRIPTIVE RESULTS OF EMPIRICAL STUDIES									
Study Phase	**Pathophysiology (No. of Articles)**	**First Author & Year**	**Geography**	**Route of Administration**	**LNG Monotherapy or Combination**	**Dosing**	**LNG Drug Name**	**PK Parameters Measured**	**Healthy Controls**
Clinical (Human) Studies	**Undernutrition** (3)	A) Nair, 1979 B) Nair, 1983 C) Nair, 1986	India	A+B) Oral C) Vaginal Ring	Combination	A) Single dose High: 500ug + 30ug EE Low: 150ug LNG + 50ug EE B) Single dose 150ug LNG + 50ug EE C) Continuous 21-35 days 60mg LNG + 30mg estradiol	A) Primovlar-30 (high) + WHO-LNB pill (low) B) WHO-LNB pill C) Unclear/generic	Cp, Cmax, Cmin, Tmax, $t_{1/2}$, CL	A+B) Yes C) No
	GI Illness (3*) * excludes 2 reviews	A) Nilsson, 1985 B) Grimmer, 1986 C) Victor, 1987	A) Sweden B) UK C) Sweden/ USA	Oral	A+B) Combination C) Monotherapy	Single dose 250ug LNG (all) + 50ug EE (A+B)	A+B) Unclear/generic C) Fillinett/Recip	Cp, BA, LNG/SHBG ratio, absorption	Yes
	Cystic Fibrosis (1)	Stead, 1987	UK	Oral and IV	Combination	Single dose 250ug LNG + 50ug EE	Ovran	Cp, BA, AUC, CL, $t_{1/2}$, Vd	Yes
	Female Genital Schistosomiasis (1)	El-Raghy, 1986	Egypt	Oral	Combination	Single dose 500ug LNG + 50ug EE	Ovral	Cp	Yes
	Uterine Fibroids (1)	Nilsson, 1982	Finland	A) IUD B) Oral	A) Monotherapy B) Combination	A) Daily release 30ug LNG B) Daily for 7 days 250ug LNG + 2mg estradiol varianate	A) Unclear/generic B) Cyclabil	Uterine tissue concentrations	No
	Lung Disease (1)	Vonk, 2021	Europe (multiple countries)	Oral	Combination	A) Single dose B) 10 consecutive days 150ug LNG + 30ug EE (all)	Microgynon	Cp, Cmax, AUC	No
	B-Cell Malignancies (1)	de Jong, 2020	Poland & Spain	Oral	Combination	Single dose 150ug LNG + 30ug EE	Unclear/generic	C_{max}, T_{max}, AUC, $t_{1/2}$	No
Pre-Clinical (Animal) Studies	**Undernutrition** (3) Rabbits	A) Prasad, 1981 B) Nair, 1981 C) Nair, 1988	India	A) Unknown B+C) IV	Monotherapy	A) Unknown B) Single dose 15-20ug LNG per kg C) Daily for 5 days 5uCi LNG + 10ug carrier LNG	Unclear/generic	Cp, Cmax, Cmin, Tmax, t1/2, CL, binding capacity, Cyt P-450 levels	Yes
	Liver Disease (1) Mice	Gommaa et al., 1983	Egypt	Oral and IV	Monotherapy	Single dose 1ug LNG	Unclear/generic	Cp, BA, AUC, CL, $t_{1/2}$, Vd	Yes

LNG: levonorgestrel
EE: ethinylestradiol
IV: intravenous
IUD: intrauterine device

Cp: plasma concentration
Cmax: maximum concentration
Cmin: minimum concentration
Tmax: time at maximum concentration

$t_{1/2}$: half-life
AUC: area under the curve
CL: clearance
Vd: volume of distribution

BA: bioavailability
SHBG: sex hormone binding globulin

KEY TAKEAWAYS

KEY TAKEAWAY 1: From the few identified studies, undernutrition consistently correlates with faster LNG clearance and shorter elimination half-lives in humans and animals, driven by altered hepatic enzyme activity and lower plasma SHBG levels. This may correspond to reduced LNG efficacy in undernourished populations and merits further investigation.

KEY TAKEAWAY 2: Intravaginal rings were found to provide steady LNG delivery and maintain consistent plasma levels without substantial variability in diverse populations.

DEFINITIONS OF UNDERNUTRITION BY STUDY TYPE

Human studies (N = 3)	Animal studies (N = 3)
Anthropometric indices: weight/height² < 0.200, triceps skinfold thickness and mid-arm circumference measured.	50% diet reduction causing 17-23% weight loss; normal hemoglobin and plasma albumin levels maintained for mild to moderate undernutrition.

ROUTES OF ADMINISTRATION

- Most clinical studies with human subjects focused on oral dosing of LNG, often in combination with other hormones such as ethinylestradiol[11,12].
- Intravaginal rings were highlighted in one human study for consistent LNG delivery over 35 days, demonstrating advantages in populations with limited health care access[13].
- Preclinical studies involving animal models used IV administration for pharmacokinetic evaluation[14,15].

UNDERNUTRITION MAY DISRUPT LNG PK, POTENTIALLY LEADING TO ALTERED DRUG EXPOSURE AND CORRESPONDING REDUCTIONS IN EFFICACY

Table 3: LNG-PK differences In undernourished populations

PK Parameter	Mean Percent Difference, undernourished vs. control
Animal studies (IV administration)[12,15]	
Metabolic clearance rate	+20%
Elimination half-life	-46%
Steady state plasma concentration	-30%
Human studies (oral administration)[13]	
Absorption half-life	+33%
Elimination half-life	-38%

LIVER FUNCTION AND HORMONE REGULATION IN UNDERNUTRITION

- Sex Hormone Binding Globulin (SHGB) is a protein produced by the liver that binds to sex hormones, such as LNG in the bloodstream and regulates the amount of free hormone in the body. Other liver proteins, such as albumin, also play a role in hormone transport.
- While SHBG levels in undernourished rabbits did not change significantly, their drug clearance rates were higher due to higher activities of liver microsomal glucuronyl transferase and cytochrome P-450 enzymes. Mean cytochrome P-450 levels were higher in rabbits who had experienced food restriction (0.934 +/- 0.308 n/moles/mg/protein) compared to healthy controls (0.648 +/- 0.130 n/moles/mg/protein)[16].
- Lower SHBG levels are often seen in undernourished individuals, potentially increasing the proportion of free LNG but also accelerating its clearance, reducing overall drug availability in humans[15].

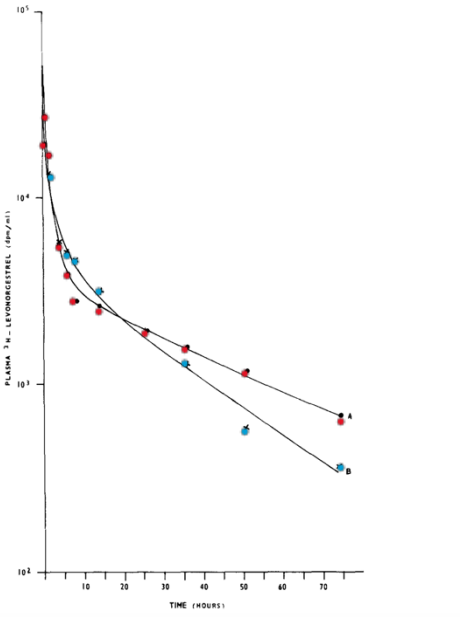


Figure 3: Plasma curves of levonorgestrel in control (red) and food restricted (blue) rabbits[15] **(ANIMAL STUDY)**

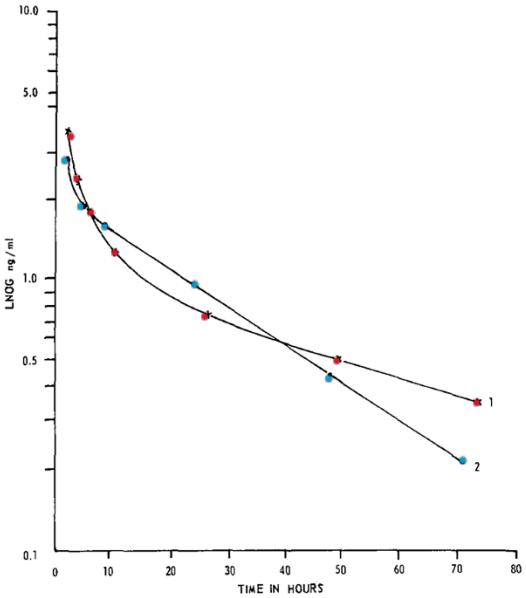


Figure 4: Plasma curves of levonorgestrel in well-nourished (red) and undernourished (blue) women[12] (**HUMAN STUDY)**

Both animal and human studies used a single dose of LNG (IV in animals, oral in humans). The plasma curves suggest a shorter terminal half-life in undernourished animals (left) and humans (right). The small sample sizes and single-dose designs limit the strength of this association.

OUTCOMES

ANIMAL STUDIES

- Studies on rabbits under restricted diets revealed increased metabolic clearance and reduced elimination half-lives. Restricted diets led to a 20% increase in metabolic clearance rate and a 30% reduction in elimination half-life of LNG[15].
- The percent of LNG doses that was excreted in urine also differed between healthy controls and undernourished rabbits and over time.
    - Single Dose % excreted in urine: controls (mean 42.5%); undernourished (mean 48.6%) [15].
    - Multiple (5) Doses % excreted in urine: controls (mean 49.6%); undernourished (mean 73.9%) [14].

HUMAN STUDIES

- Faster clearance rates and shorter elimination half-lives of LNG were observed in undernourished Indian women. Undernourished women showed a two-phase plasma concentration decline, indicating altered drug distribution compared to the three-phase pattern in well-nourished women[11,12].

- Undernutrition modifies the pharmacokinetics of levonorgestrel, leading to faster drug clearance but steady delivery from intravaginal rings ensures sufficient drug levels to inhibit ovulation, even in undernourished women[13].

LIMITATIONS OF PK STUDIES IN UNDERNOURISHED POPULATIONS

1. **Geographic scope and methodological concerns:** All undernutrition studies were conducted in India, potentially limiting the generalizability of findings to other regions and populations. Additionally, all studies were conducted by Nair et al., raising concerns about potential bias, reproducibility, and broader applicability particularly as the Fotherby review[2] questioned the validity of methods used in the earliest study published by this team due to their findings being dissimilar from other studies.

2. **Sample sizes:** Many studies, particularly animal studies, had small sample sizes, limiting statistical power and reliability. For example, rabbit studies often included an N=12 animals with six per group, while human studies included between 11-18 participants.

3. **Heterogeneity in methods:** Differences in study designs, such as dosing regimens and PK measurement techniques, contribute to variability in results. Animal studies used IV administration with single or daily dosing, while human studies focused on single-dose oral or IV regimens. Variations in PK assessment methods further complicate comparisons and limit the integration of findings across studies.

4. **Nutritional Assessment Methods:** Most notably, human studies provide inconsistent measures of nutritional status, with significant variability in methodology and participant characteristics, relying on proxies like anthropometric measures and socioeconomic status and lacked biochemical validation. This limits accuracy in capturing metabolic changes. For example, a healthy mid-upper arm circumference (MUAC) for women, a measurement that can indicate nutritional status, is generally considered to be greater than 22 cm[17]. One study by reported a mean MUAC of 26.6 cm for controls and 22.1 cm for the undernourished group, with only 5 out of 9 individuals in this group meeting the <22cm classification of undernourished[12]. Another study used women from a low socioeconomic group (earning less than $8 USD per month), noting some anthropometric signs of undernutrition but no biochemical changes as women's blood hemoglobin and plasma albumin levels remained normal[11]. Finally, an intravaginal ring (IVR) study involving 18 women included 3 subjects with a healthy weight-to-height ratio and MUAC limiting precision for findings related to undernourished women. Future studies should consider clear inclusion and exclusion criteria, in addition to including markers like serum albumin and SHBG for better insights and accuracy for specific undernourished populations.

IMPLICATIONS

Dose adjustments for undernourished populations: From the six identified studies, undernutrition appears to alter LNG PK parameters including accelerated LNG clearance. Adjusted dosing in undernourished populations may be needed to maintain contraception effectiveness. One study suggested that dosing adjustments should be considered for populations where nutritional deficiencies are prevalent[12]. However, as all women in a population are unlikely have the same nutritional profile, dosing adjustments are likely more appropriate at the individual level, following individualized assessment.

Equity in contraceptive access: Intravaginal rings offer a reliable method for consistent LNG delivery, especially in resource-limited settings. Intravaginal delivery systems were found to be less prone to variability and can improve contraceptive reliability in diverse populations[13]. However, their success depends on addressing cultural acceptability, affordability, and awareness barriers in resource-limited settings. Additionally, challenges such as ring expulsion should be considered when recommending IVRs for LMICs, as these issues could impact their effectiveness and user adherence.

KEY TAKEAWAYS

KEY TAKEAWAY 1: There is a dearth of levonorgestrel (LNG) pharmacokinetic (PK) data in populations with infectious and non-infectious gastrointestinal illnesses, highlighting an abundant need to learn more about potential PK changes related to these conditions which are a leading burden of disease in LMICs[18].

KEY TAKEAWAY 2: Although existing PK studies in patients with inflammatory bowel disease have several limitations, different trends in key PK parameters (plasma concentrations, bioavailability, volume of distribution) were observed. Non-significant results should be interpreted with caution due to the small sample sizes in each of these studies.

RELEVANT PUBLICATIONS (N = 5)

Articles published between **1985 – 2010**

Study designs include:
- Human PK Study (n = 3)
- Commentary (n = 1)
- Systematic Review (n = 1)

Sweden, United States, & United Kingdom

Table 4: LNG PK differences in ileostomy/ulcerative colitis participants relative to healthy controls, *p<0.05 [19,20].

Route	Parameter	% change in means, ileostomy vs. controls
IV	AUC*	+ 45.9%
Oral	AUC	+ 13.9%
	Bioavailability	- 18.5%
	Volume of distribution	- 15.3%
	10-H Plasma level	-25.0%
	10-H Plasma level*	+ 54.5% (u.colitis pre-op)

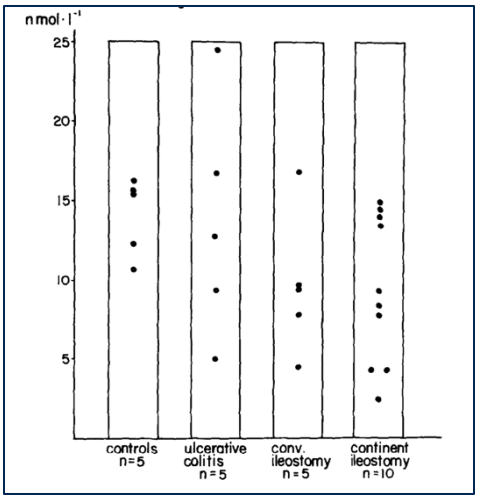


Figure 5: Peak LNG plasma levels in different groups (L-R: healthy controls, mild ulcerative colitis, conventional ileostomy, continent ileostomy)[19].

MULTIPLE LNG PK PARAMETERS APPEAR TO HAVE DIFFERENT TRENDS IN POPULATIONS WITH GI ILLNESS WHEN COMPARED TO HEALTHY CONTROLS.

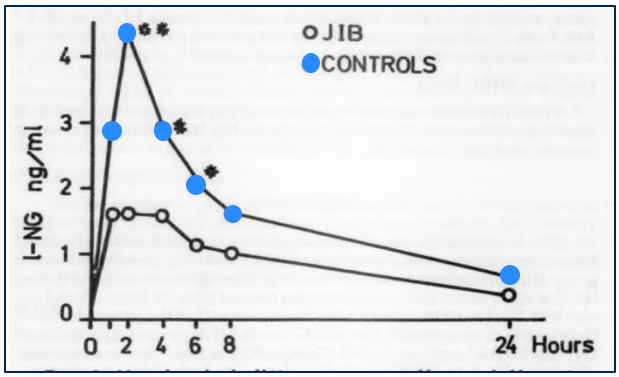


Figure 6: Mean plasma levels of LNG in patients operated by jejeunoileal bypass (open circles) and controls (blue circles) after oral 0.25mg LNG. **p<0.01, *p<0.05[21]

LIMITATIONS OF EXISTING LNG PK STUDIES IN POPULATIONS WITH GI ILLNESS

The potential impact of GI illnesses is difficult to ascertain as studies focused on participants with well-controlled inflammatory bowel disease (IBD) or inflammation of the large intestine (e.g., Ulcerative Colitis), despite LNG absorption occurring primarily in the small intestine[22]. No data on LNG-PK and enteric infections or uncontrolled IBD was identified. In addition, existing PK studies in populations with GI illnesses have very small sample sizes risking type II errors (false-negatives), rarely assess LNG alone, have only been conducted in high-income settings limiting generalizability to LMICs, and are of too short duration to assess variation during the menstrual cycle and/or efficacy (e.g., unintended pregnancy).

- **Single dose only**
- **Oral or IV formulations only**
- **LNG + EE combinations mostly**
- **Small sample sizes** (5-6 participants per group)
- **High-income settings only**
- **Non-infectious, well-controlled GI illnesses only**

EE: Ethinylestradiol

OTHER RESULTS

The six conditions discussed in this section were consolidated due to limited literature, with only one article identified for each. These conditions were independently assessed for potential alterations in LNG pharmacokinetics.

KEY TAKEAWAYS

KEY TAKEAWAY 1: Despite the importance of liver function in LNG metabolism and some LNG administration occurring via the reproductive tract, only one study investigated LNG PK in human populations with liver or reproductive tract abnormalities. This surprising shortage of data underscores a major gap and opportunity for further research in LMIC contexts given the high global burden of chronic liver diseases[18]

KEY TAKEAWAY 2: While available LNG PK data in special populations can be used to inform model development, the scarcity of healthy control groups for baseline comparison poses challenges in assessing impact magnitude of a particular altered physiology on LNG PK and efficacy.

Table 5: Notable LNG PK differences in special populations beyond undernutrition and GI illness

Cystic Fibrosis	Liver Disease	Schistosomiasis	Uterine Fibroids	Lung Disease & B-Cell Malignancies
IV-administered LNG cleared faster in cystic fibrosis patients than healthy controls*[23] (Figure 7, Table 4)	Mice with induced hepatic necrosis had faster clearance, shorter half-life, and lower AUC than healthy mice[24]	Early schistosomiasis showed no differences, unsurprising without liver impairment or genital scarring. Studies on advanced stages may yield greater insights[25]	2/9 participants with severe fibroids expelled IUDs pre-hysterectomy, suggesting potential efficacy impact[26]	No healthy controls for PK comparison[27,28]

Cystic Fibrosis

- Evidence that cystic fibrosis (CF) can impact absorption and disposition of drugs and their metabolites, likely driven by GI comorbidities[29,30]
- Cystic fibrosis likely underreported and underdiagnosed in LMICs[31]
- LNG plasma exposure after IV administration of Ovran (LNG-EE2) decreased more rapidly in **cystic fibrosis** patients than in healthy controls, although not to a statistically significant degree. There were no differences with oral administration (Figure 7, Table 4)[23]
- Need for additional, larger studies in CF patients to confirm these preliminary observations

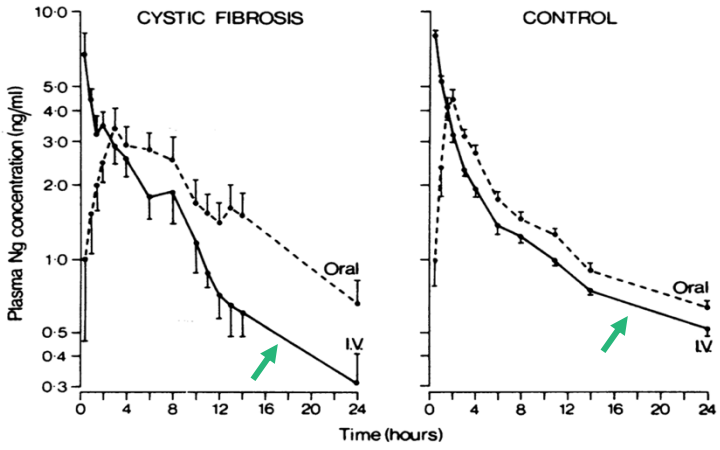


Figure 7: Mean plasma levonorgestrel concentrations after oral and IV administration of 250ug in six patients with cystic fibrosis and five controls*[22]

Table 6: Percent difference in means for reported LNG PK parameters in cystic fibrosis patients relative to healthy controls*[23]

Route	Parameter	% change in means, CF vs. control *
Oral	AUC	+ 18.3%
IV	AUC	+ 12.2%
	$t_{1/2}$	- 31.9%
	CL	+ 45.5%
	Vd	- 13.3%
Both	BA	+ 8.6%

*data found to be statistically insignificant by authors and should be interpreted with caution due to small sample sizes

Liver Disease

- Impaired liver function is known to impact drug PK and ADME metabolism, potentially reducing efficacy as a result[32,33]
- Evidence that accounting for physiological differences of patients with hepatic impairment, e.g. liver cirrhosis, is important for ensuring accuracy of PBPK model simulations[34]
- LMICs have high prevalence and mortality of liver diseases like Hepatitis B and C, and fewer than 20% are aware of their diagnosis[6,35]
- A single pre-clinical *in vivo* study found that LNG in mice with **induced hepatic necrosis** had 20% higher clearance and 12% shorter elimination half-life than in healthy mice. AUC and plasma concentrations were also lower in necrotic mice, although not to a statistically significant degree[24]
- These data suggest that hepatic impairment and hepatotoxic drugs may alter LNG pharmacokinetics, but further studies in humans with diverse liver diseases are needed to confirm and elucidate this effect

MAJOR GAP AND NEED FOR ADDITIONAL STUDIES IN POPULATIONS WITH IMPAIRED LIVER FUNCTION

Schist-osomiasis

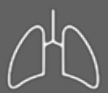
- 16-56 million girls live with female genital schistosomiasis (FGS), which can cause liver enlargement or disease and scarring of genital tissues[36]
- A single study in Egypt found little evidence that LNG elimination is impacted by **early-stage schistosomiasis**, unsurprising given limited liver impairment or other pathophysiological changes in early disease stages. The only notable difference was higher LNG plasma concentrations in groups who had been utilizing oral contraceptives (OC) for 6 months prior to the study. These differences were likely attributable to the OC use rather than any changes that could impact LNG PK[25]
- Larger studies with longer follow-up are needed in advanced schistosomiasis and FGS specifically, where physiological changes/liver disease and scarring are likely more pronounced

Uterine Fibroids

- High prevalence and DALYs from uterine fibroids in low-middle income regions[37]
- A study in Finland measured LNG concentrations in reproductive tissues post-hysterectomy in women with severe uterine fibroids or menorrhagia . Absence of healthy controls and limited PK data preclude definitive conclusions about fibroid effects on LNG. pharmacokinetics. However, IUD expulsion in two participants pre-hysterectomy suggests potential reduced efficacy in this population[26]
- Need for additional studies in conditions that can damage reproductive tissues (e.g. fibroids, pelvic inflammatory disease, ectopic pregnancy)

Impact on LNG PK unclear in drug-drug interaction (DDI) studies that lack healthy controls

Lung Disease



- Chronic respiratory illnesses are a significant contributor to disability-adjusted life years (DALYs) and deaths in low- and middle-income countries[38]
- Co-administration of Nintedanib in European patients with **Systemic Sclerosis-Associated Interstitial Lung Disease** (Ssc-ILD) did not impact plasma exposure of Microgynon (LNG + EE), and therefore is not expected to reduce contraception effectiveness[27]
- Impact of Ssc-ILD on LNG PK is unclear without comparison to healthy controls

B-Cell Malignancies

- LMICs bear a disproportionate burden of cancer with less access to preventative measures, resources, and care than high-income settings[39]
- Ibrutinib co-administration in patients with B-cell malignancies did not alter the PK of LNG-EE2 in patients with B-cell malignancies, suggesting no reduction in contraceptive efficacy[28]
- Lack of healthy controls precludes definitive conclusions on malignancies' impact on LNG PK
- Possible need for further investigation of LNG PK in patients with various forms of cancer

DISCUSSION

This scoping review sought to:

1. Map the existing literature on LNG in populations with altered physiology (e.g. undernutrition, liver disease, female reproductive tract abnormalities, and GI illnesses) that could plausibly alter drug absorption, distribution, metabolism, or excretion.
2. Identify any gaps in the literature or existing data.
3. Identify relevant PK data that could be used to inform LNG physiologically based pharmacokinetic (PBPK) models for different populations.

KEY TAKEAWAYS

KEY TAKEAWAY 1: There is a scarcity of levonorgestrel (LNG) pharmacokineticcycle anda for multiple special populations. This highlights an abundant opportunity to learn more about potential pharmacokinetic changes in special populations with altered physiology that may plausibly impact absorption, distribution, metabolism, and excretion (ADME) processes.

- Limited data was found for populations with: undernutrition, inflammatory bowel diseases, liver disease, lung disease, uterine fibroids, and b-cell malignancies.
- No data was found for populations with: enteric diseases, schistosomiasis (late-stage), or structural reproductive abnormalities related to pelvic inflammatory disease/ectopic pregnancy/pelvic adhesions/pelvic venous disorders.

KEY TAKEAWAY 2: Current data suggests potentially different pharmacokinetic profiles of LNG among undernourished populations and those with gastrointestinal illnesses. However, additional investigation is needed for these conditions along with other prevalent conditions in low- and middle-income countries (LMICs) that may affect ADME processes.

- **Undernutrition**: undernutrition appears to impact multiple LNG-PK parameters in both clinical and pre-clinical studies, although all identified research appears to have been conducted by the same research team and could benefit from reproduction in different geographies and/or by other research teams.
- **GI Illnesses:** despite multiple limitations identified with existing LNG-PK studies in populations with GI illnesses, multiple LNG PK parameters appear to have different trends, some of which were significantly different from controls in groups with ulcerative colitis and partial bowel resections. Longer and larger studies are needed to better understand the impact of these differences on LNG efficacy in these populations and others with GI illnesses.

KEY TAKEAWAY 3: Due to insufficient data and methodological limitations, LNG physiologically based pharmacokinetic (PBPK) models may be less precise for particularly vulnerable populations in LMICs where different and overlapping disease burdens may impact LNG efficacy.

- **Sampling:** Very small sample sizes and corresponding low power reduce the likelihood that studies in these special populations will detect a true effect. Correspondingly due to the voluntary nature of many of these studies and often unclear inclusion and exclusion criteria the generalizability of these findings to the broader special population group is likely limited.
- **Duration:** a majority (60%) of identified empirical PK studies assessed a single dose of LNG or LNG—combined contraception. This short study duration limits understanding of potential variation in PK parameter estimates which can vary throughout the menstrual cycle and may further reduce the precision of estimates.
- **Data Heterogeneity**: variation in plasma sampling times both within (e.g., different sampling times for controls vs. cases) and between studies, different LNG doses, and procedures (e.g. fasting before oral LNG administration) limits the comparability of results and our understanding of the true effect of these conditions on LNG PK.

Although the specific focus of our review reveals potentially important gaps for multiple special populations, it is important not to lose sight of the broader landscape of contraception use and access, particularly in LMICs, where the 2015-19 rate of unintended pregnancies was almost double that of high-income countries[40,41].

DISCUSSION CONT'D

Despite a majority of our identified empirical PK studies in special populations occurring over thirty years ago, there appears to have been renewed interest in the role of abnormal physiology on drug PK particularly for populations in LMICs with different disease burdens. A 2021 systematic review assessing the effects of undernutrition on the PK of medications for tuberculosis, malaria, neglected tropical diseases (NTDs), and human immunodeficiency virus (HIV) identified over 21 drugs with PK alterations due to undernutrition, along with a dearth of data for populations with overlapping conditions (i.e. severe undernutrition and NTDs)[8]. Similarly, a 2024 meta-analysis revealed that treatment of malaria using artemisinin-based combination therapies was more likely to fail in children with acute undernutrition due to altered drug absorption and metabolism (adjusted hazard ratio 1.14, 95% CI 1.02-1.26, p=0.016)[42]. In higher-income settings, different review articles have also highlighted alterations in antibiotics PK profiles among older populations and people who inject drugs[43,44]. All of the studies highlighted a need for additional PK studies in special populations to help optimize pharmaceutical dosing and treatment efficacy.

In LMICs, effective dosing of LNG or other hormonal contraception is particularly important, especially as the women of reproductive age who are most vulnerable are more likely to be affected by one or more condition of poverty (e.g. undernutrition, liver disease, NTDs, etc.). Ensuring that these women have access to contraception and that it is effective in preventing an unintended pregnancy is an equity issue that deserves additional attention and further investigation. Lastly, clinically relevant drug interactions for LNG with some antiretrovirals and tuberculosis treatments highlight other potentially impactful interactions to consider for special populations with overlapping disease burdens[45,46].

Limitations

Our review was limited to four databases, three for peer-reviewed literature and one drug regulatory agency data, and a single hormonal contraceptive. Due to time limitations, only data for non-oral formulations of LNG from the U.S. FDA was reviewed. However, as most of our peer-reviewed literature included oral dosing and the U.S. FDA database appeared to have the richest PK data of the six regulatory agencies we explored, we believe we were able to minimize bias in our review. As discussed throughout this report and identified by previous reviews, in general there is limited quality evidence regarding special population groups and LNG-PK data, limiting our understanding of this topic and the potential impact of these conditions.

MOVING FORWARD: OPPORTUNITIES & CONSIDERATIONS

APPRAISE: Our review was limited to levonorgestrel. Expanding on this review to consider other hormonal contraceptives and drug-drug interactions could increase overall comprehension of this issue.

EXPERIMENT(S): Our review identified abundant opportunity to support or conduct further hormonal contraception PK research in comparative studies with special population groups.

DIVERSIFY: Initial clinical PK studies for levonorgestrel have largely been conducted in healthy women in high-income countries. PK data could be more inclusive if these of global populations by diversifying study geography and inclusion criteria.

PROJECT TEAM

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APPENDIX 1

The following figure provides a high level summary of levonorgestrel pharmacokinetic action along with the various conditions that could plausibly alter levonorgestrel pharmacokinetic action, as theorized by the study team and/or suggested in the literature.

CONDITIONS THAT COULD ALTER LNG ACTION

Absorption

- **ORAL:** absorbed via the GI tract (small intestine) *impacted by* **GI ILLNESSES**
- **IUD:** absorbed via the endometrium *impacted by* **FEMALE REPRODUCTIVE TRACT PATHOLOGY**
- **SUBDERMAL:** absorbed into interstitial fluids

Distribution

- **ORAL:** binds to plasma proteins to reach target organs *impacted by* **UNDERNUTRITION**
- **IUD:** acts locally on reproductive organs *impacted by* **ALTERED BLOOD FLOW &/ STRUCTURAL ABNORMALITIES**
- **SUBDERMAL:** binds to plasma proteins to reach target organs *impacted by* **UNDERNUTRITION**

Metabolism

- **LIVER DISEASE(S)**
- **NUTRITIONAL STATUS** (up/down regulation of CY3A4 & CYP3A5[47])

Per a 2020 Systematic Review[47]:

- weight loss increased CYP3A4 activity
- obesity might decrease CYP3A4/5 activity[47] & may reduce LNG efficacy[3]

Excretion

- **RENAL DISEASE**

Reduced renal function could impact drug excretion & corresponding exposure[48]

SUBJECT MATTER EXPERT

A subject matter expert from the University of Washington reviewed the findings summarized in this report for credibility.

CONSULTED SUBJECT MATTER EXPERT
Dr. Samuel Arnold • Assistant Professor of Pharmaceutics • Expertise in Drug Discovery, In vitro to in vivo extrapolation, Infectious Diseases, Intestinal Surgery and GI Diseases, Microphysiological organ systems, Pharmacokinetics-Pharmacodynamics, Pharmacology, Simulation Modeling, Translational Research

APPENDIX 2

Table S1: PubMed Search Strings. All disease terms combined with levonorgestrel and pharmacokinetics terms.

Concept	Search String
Levonorgestrel	("levonorgestrel"[MeSH Terms] OR levonorgestrel [Title/Abstract]) AND (oral OR intramuscular OR subcutaneous OR intrauterine OR transdermal OR vaginal OR implant OR IUD OR intrauterine devices medicated OR birth control)
Pharmacokinetics	("Pharmacokinetics"[MeSH Terms] OR "Pharmacokinetics"[MeSH Subheading] OR "pharmacokinetic*"[Title/Abstract] OR "drug kinetic*"[Title/Abstract] OR "volume of distribution"[Title/Abstract] OR "Cmax"[Title/Abstract] OR "peak concentration*"[Title/Abstract] OR "peak time*"[Title/Abstract] OR "Tmax"[Title/Abstract] OR "AUC"[Title/Abstract] OR "area under the curve"[Title/Abstract] OR "t1 2"[Title/Abstract] OR "half life*"[Title/Abstract] OR "kinetic profile*"[Title/Abstract] OR "bioavailabilit*"[Title/Abstract] OR "biological availabilit*"[Title/Abstract] OR "biologic availabilit*"[Title/Abstract] OR "tissue distribution*"[Title/Abstract] OR "protein binding"[Title/Abstract] OR "absorption, physiological"[MeSH Terms] OR "absorption"[Title/Abstract] OR "Metabolic Clearance Rate"[MeSH Terms] OR "clearance"[Title/Abstract] OR "elimination"[Title/Abstract] OR "excretion"[Title/Abstract] OR "PK"[Title/Abstract])
Liver Disease	("Liver Diseases"[MeSH Terms] OR "Liver Disease"[Title/Abstract] OR "Liver Dysfunction"[Title/Abstract] OR "Liver Failure"[MeSH Terms] OR "Liver Failure"[Title/Abstract] OR "Hepatitis"[MeSH Terms] OR "hepatitis*"[Title/Abstract] OR "Liver Inflammation"[Title/Abstract] OR "Liver Cirrhosis"[MeSH Terms] OR "Liver Cirrhosis"[Title/Abstract] OR "Liver Fibrosis"[Title/Abstract] OR "Nonalcoholic Fatty Liver Disease"[Title/Abstract] OR "NAFLD"[Title/Abstract] OR "Alcoholic Liver Disease"[Title/Abstract] OR "Fatty Liver"[Title/Abstract] OR "Fatty Liver"[Title/Abstract] OR "Hepatitis B"[MeSH Terms] OR "Hepatitis C"[MeSH Terms] OR "Chronic Hepatitis"[Title/Abstract] OR "liver cirrhosis, biliary"[MeSH Terms] OR "liver cirrhosis, alcoholic"[MeSH Terms] OR "Cirrhosis"[Title/Abstract] OR "Liver Injury"[Title/Abstract] OR "Liver Regeneration"[Title/Abstract] OR "Liver Enzymes"[Title/Abstract] OR "Fibrosis"[MeSH Terms] OR "Liver Microbiome"[Title/Abstract] OR "Liver Inflammation"[Title/Abstract] OR "Hepatic Steatosis"[Title/Abstract])
Infectious Diarrheal Diseases	("Diarrhea"[MeSH Terms] OR "diarrhoea"[Title/Abstract] OR "Infectious Diarrhea"[Title/Abstract] OR "Chronic Diarrhea"[Title/Abstract] OR "diarrhea acute"[Title/Abstract] OR "gastroenteritis"[MeSH Terms] OR "gastroenteritis"[Title/Abstract] OR "Rotavirus"[MeSH Terms] OR "Rotavirus"[Title/Abstract] OR "Escherichia coli"[MeSH Terms] OR "E.coli"[Title/Abstract] OR "Salmonella"[MeSH Terms] OR "Salmonella"[Title/Abstract] OR "Shigella"[MeSH Terms] OR "Shigella"[Title/Abstract] OR "Campylobacter"[MeSH Terms] OR "Campylobacter"[Title/Abstract] OR "Norovirus"[MeSH Terms] OR "Norovirus"[Title/Abstract] OR "Giardiasis"[MeSH Terms] OR "giardia*"[Title/Abstract] OR "dysentery, amebic"[MeSH Terms] OR "dysentery amebic"[Title/Abstract] OR "frequent stools"[Title/Abstract] OR "Clostridium Infections"[MeSH Terms] OR "C.difficile"[Title/Abstract] OR "Vibrio cholerae"[MeSH Terms] OR "Persistent Diarrhea"[Title/Abstract] OR "Traveler's Diarrhea"[Title/Abstract] OR "Entamoeba histolytica"[MeSH Terms] OR "Entamoebiasis"[MeSH Terms])
Undernutrition	(“Malnutrition"[Mesh:NoExp] OR "Severe Acute Malnutrition"[Mesh] OR "Starvation"[Mesh] OR "Protein-Energy Malnutrition"[Mesh] OR undernutrition*[tiab] OR undernutrition*[tiab] OR "deficient nutrition"[tiab] OR malnourishment*[tiab] OR undernourishment*[tiab] OR underfeeding*[tiab] OR nutritional deficien*[tiab] OR marasmus[tiab] OR kwashiorkor[tiab] OR starvation*[tiab] OR famine*[tiab] OR stunting[tiab] OR wasting[tiab] OR underweight[tiab])

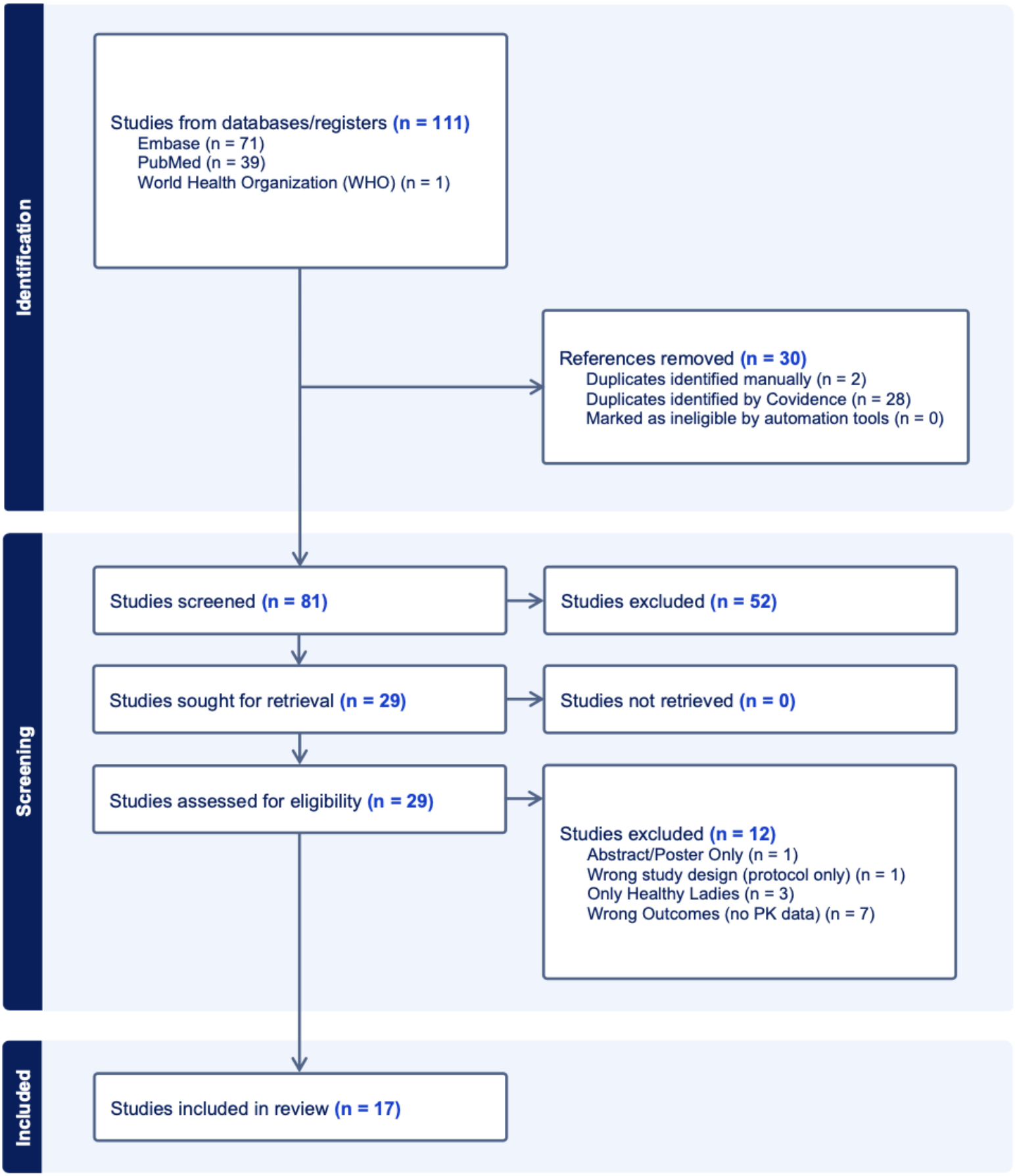
APPENDIX 2

Table S1: PubMed Search Strings. All disease terms combined with levonorgestrel and pharmacokinetics terms.

Concept	Search String
Pelvic Scar Tissue, Adhesions, & Venous Disorders	("Pelvis"[Mesh] OR pelvis[Title/Abstract] OR pelvic[Title/Abstract] OR "Pelvic Adhesions"[tiab] OR pelvic adhesions[Title/Abstract] OR pelvic scar tissue[Title/Abstract]) AND ("Venous Insufficiency"[Mesh] OR "Venous Reflux"[tiab] OR "Varicose Veins"[Mesh] OR vein insufficiency[Title/Abstract] OR venous reflux[Title/Abstract] OR varicose veins[Title/Abstract] OR venous incompetence[Title/Abstract] OR venous syndrome[Title/Abstract] OR "congestion syndrome"[Title/Abstract] OR venous disease[Title/Abstract] OR venous disorder[Title/Abstract] OR vein disorder[Title/Abstract] OR venous insufficiency[Title/Abstract] OR varicose veins[Title/Abstract])
Pelvic Inflammatory Disease	((("Pelvic Inflammatory Disease"[Mesh] OR "pelvic inflammatory disease"[tiab] OR pelvic inflammatory disorders[tiab] OR PID[tiab] OR "adnexitis"[tiab] OR "salpingitis"[tiab] OR "oophoritis"[tiab] OR "endometritis"[tiab] OR "pelvic peritonitis"[tiab] OR "tubo-ovarian abscess"[tiab]))
Uterine Fibroids	("Leiomyoma"[Mesh] OR "Uterine Neoplasms"[Mesh:NoExp] OR fibroid*[tiab] OR leiomyoma*[tiab] OR myoma*[tiab] OR fibroma*[tiab] OR fibroids[tiab] OR "uterine tumor"[tiab] OR "uterine tumour"[tiab] OR "uterine tumors"[tiab] OR "uterine tumours"[tiab])AND("uterus"[MeSH] OR "uterine"[tiab] OR "intrauterine"[tiab] OR "uterus"[tiab])
Schistosomiasis	("Schistosomiasis"[Mesh] OR "Schistosoma"[Mesh]) AND ("Female Genital Diseases"[tiab] OR "Genital Diseases, Female"[Mesh]) OR "female genital schistosomiasis"[Title/Abstract] OR "FGS"[Title/Abstract] OR (("schistosomiasis"[Title/Abstract] OR "schistosoma"[Title/Abstract] OR "bilharzia"[Title/Abstract]))
Non-infectious Diarrheal Diseases	("Diarrhea"[MeSH Terms] OR "diarrhoea"[Title/Abstract] OR "Chronic Diarrhea"[Title/Abstract] OR "diarrhea, acute"[Title/Abstract] OR "Frequent stools"[Title/Abstract] OR "Irritable Bowel Syndrome"[MeSH Terms] OR "Irritable Bowel Syndrome"[Title/Abstract] OR "IBS"[Title/Abstract] OR "Crohn Disease"[MeSH Terms] OR "Crohn's Disease"[Title/Abstract] OR "Colitis, Ulcerative"[MeSH Terms] OR "Ulcerative Colitis"[Title/Abstract] OR "Inflammatory Bowel Diseases"[MeSH Terms] OR "Inflammatory Bowel Disease"[Title/Abstract] OR "Colitis, Microscopic"[MeSH Terms] OR "Microscopic Colitis"[Title/Abstract] OR "Chronic Functional Diarrhea"[Title/Abstract] OR " Gastrointestinal Diseases"[MeSH Terms] OR "Functional Gastrointestinal Disorder"[Title/Abstract] OR “Gastrointestinal Diseases” [Title/Abstract] OR "Gastrointestinal motility disorders"[Title/Abstract] OR "Irritable Bowel Disease"[Title/Abstract] OR "Celiac Disease"[MeSH Terms] OR "Celiac Disease"[Title/Abstract] OR "Fecal Incontinence"[MeSH Terms] OR "Fecal Incontinence"[Title/Abstract] OR "Colorectal Disease"[Title/Abstract] OR "Chronic diarrhea"[Title/Abstract])
Ectopic Pregnancy	("pregnancy, ectopic"[MeSH Terms] OR "ectopic pregnancy"[Title/Abstract] OR "tubal pregnancy"[Title/Abstract] OR "extrauterine pregnancy"[Title/Abstract] OR "ecdysis"[Title/Abstract])

Searches were translated for Embase and Global Index Medicus.
ChatGPT was also used to help generate additional concept terms.

COVIDENCE PRISMA FLOWCHART



In addition to the peer-reviewed literature captured in the PRISMA flowchart, we search the FDA database for PK data in special populations for non-oral LNG formulations.

LIST OF 17 ARTICLES INCLUDED IN THE REVIEW

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