

BMJ Open Scoping review to map evidence on mechanism of action, pharmacokinetics, effectiveness and side effects of centchroman as a contraceptive pill

Rita Kabra,¹ Komal Preet Allagh ,² Moazzam Ali ,¹ Chandani Anoma Jayathilaka,³ Kasonde Mwinga,⁴ James Kiarie¹

To cite: Kabra R, Allagh KP, Ali M, *et al.* Scoping review to map evidence on mechanism of action, pharmacokinetics, effectiveness and side effects of centchroman as a contraceptive pill. *BMJ Open* 2019;**9**:e030373. doi:10.1136/bmjopen-2019-030373

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-030373>).

Received 11 March 2019
Revised 27 August 2019
Accepted 02 September 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

²Consultant, World Health Organization, Geneva, Switzerland

³Department of Family Health, Gender and Life course, World Health Organization Regional Office for South-East Asia, New Delhi, India

⁴World Health Organization Country Office for India, New Delhi, India

Correspondence to

Dr Komal Preet Allagh;
komal.allagh@gmail.com

ABSTRACT

Objective To systematically identify and map the available evidence on effectiveness, side effects, pharmacokinetics and mechanism of action of centchroman as a contraceptive pill.

Introduction Centchroman was introduced in the Indian national family planning programme in 2016 as a once-a-week short-term contraceptive pill/oral contraceptive. At present there are no WHO recommendations on this method of contraception. We examined the available evidence through a scoping review.

Methods A search was conducted inclusive to the years 1970–2019 on electronic databases, grey literature sources and reference lists of included studies to identify studies. The five stages of Arksey and O'Malley's scoping review framework were applied in undertaking this scoping review.

Results The review identified 33 studies conducted between 1976 and 2017. Two studies reported mechanism of action of centchroman. Pharmacokinetics was reported by five studies among non-breastfeeding women and four studies among breastfeeding women. Eight studies reported on effectiveness ranging from 93% to 100%. Pregnancies due to user failure ranged from 2.6% to 10.2%. Although side effects were reported in 13 studies, the incidence varied greatly between the studies. Continuous bleeding and prolonged cycles >45 days were the most commonly reported side effects. All studies conducted had a small sample size and the duration of follow-up of women was 12 months or less. Fifty-five per cent of studies were by the developers of the pill (Central Drug Research Institute) and results of the phase IV clinical trial were unavailable.

Conclusions The scoping review shows that studies with robust designs and conducted in international context are lacking. Insufficient evidence exists on centchroman use as a postcoital contraceptive pill. The broad uncertainty in range of side effects and effectiveness in the studies implies insufficient evidence to make global recommendations on centchroman that is currently licensed as a contraceptive in India.

INTRODUCTION

Centchroman acts as a selective oestrogen receptor modulator with tissue selective

Strengths and limitations of this study

- Strength of our study is that it is the first scoping review to explore the mechanism of action, pharmacokinetics, effectiveness and side effects of centchroman, when used as a weekly or postcoital contraceptive pill.
- A limitation of our review is that we are likely to have missed studies on mechanism of action of centchroman since animal studies were excluded from the review.
- All identified studies in this scoping review were from India. Additionally, roughly half of the studies in this review were published from the developers of the drug (Central Drug Research Institute).
- There is no detailed drug trial on use of centchroman as a postcoital contraceptive pill.
- Studies on side effects of centchroman as a contraceptive pill are limited by small sample size, short duration of follow-up and the fact that all studies have been conducted in India.

oestrogenic or antiestrogenic effects.¹ It suppresses the oestrogen receptors in the reproductive organs, but stimulates those of other organs like the bones.^{1 2} It is used as a contraceptive pill/oral contraceptive and in treatment of dysfunctional uterine bleeding, mastalgia and fibroadenoma due to its oestrogen antagonist effect.³ Due to its oestrogen agonist effect, centchroman is used for management of osteoporosis and its levoisomer has been shown to have some cardioprotective effects.³ The reported advantages of centchroman over other contraceptive pill/oral contraceptives are: (1) it is taken once a week; (2) it does not have any side effects seen with hormonal pills like nausea, vomiting and weight gain; (3) it is considered safe for use among breastfeeding women⁴; and (4) it can be taken by women of all ages.

In the 1960s, the Government of India called on Indian laboratories to develop alternate

birth control pills. The team at Central Drug Research Institute (CDRI) took up this challenge and synthesised^{3,5} centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-p(β-pyrrolidinoethoxy)-phenyl-7-methoxychroman) in 1967.^{3,6} Since it was made at CDRI and belongs to the chroman family, it was named as centchroman. In 1994, centchroman was given an international non-proprietary name as ormeloxifene.⁷ Following preclinical and clinical studies (phase 1 and 2) in 1989 the Drug Controller General of India approved centchroman as a contraceptive pill/oral contraceptive in 1991.^{3,6} It was available in the Indian market since 1992. It was first manufactured by Torrent Pharmaceuticals, Ahmedabad, and marketed under brand name Centron. Later, Hindustan Latex Limited (HLL) Lifecare, Thiruvananthapuram, manufactured it under the brand names Choice-7 and Saheli.⁸ The Ministry of Health and Family Welfare, India, has distributed centchroman at a subsidised cost since 1995 (social marketing scheme).^{3,6}

In 2008, HLL Lifecare entered the international market by launching centchroman as a postcoital pill under the brand name Ivyfemme in Peru, South America.⁹ However, in 2010 the licence to sell the pill was revoked by Peru's Directorate General of supplies and drugs. The reason given for this was that the pill acted by preventing implantation of a fertilised egg and sale of any abortifacient drug was considered illegal in Peru.⁹ In 2013, HLL Lifecare launched centchroman as a postcoital pill in India under the brand name Tatkal-72.¹⁰ The production of Tatkal-72 was discontinued in 2014 due to restrictions on marketing and advertising of emergency contraceptive pills in India.

The Ministry of Health and Family Welfare, India, in April 2016 decided to expand oral contraceptive options by including centchroman in the national family planning programme under the brand name *Chhaya*.^{4,5,11} Chhaya is available to women through the public delivery system free of cost. Oral contraceptives that are safe among breastfeeding women have a better potential to improve the use of family planning methods by postpartum women, hence centchroman was included in the national family planning programme. Figure 1 depicts the key milestones in the evolution of centchroman in India.

In this review we have focused on the use of centchroman as an contraceptive pill/oral contraceptive (weekly pill and postcoital pill). As a weekly contraceptive pill, the recommended dosage of centchroman is a 30 mg pill twice a week for 12 weeks, followed by a 30 mg pill once a week.^{4,5} Centchroman as an emergency postcoital pill is taken as a 60 mg dose within 72 hours of intercourse.¹²

We are conducting this scoping review to determine the scope/coverage of the body of literature on effectiveness, safety, pharmacokinetics and mechanism of action of centchroman as a contraceptive pill (weekly and postcoital). This review will identify and map the types of available evidence on centchroman as a contraceptive pill and determine any knowledge gaps.

Aims and objectives

This scoping review aims to systematically include the entire range of published and grey literature on:

- ▶ Extent and type of evidence on effectiveness and side effects of using centchroman as a contraceptive pill (weekly and postcoital pill).
- ▶ Extent of evidence on mechanism of action of centchroman when used as a contraceptive in women.
- ▶ Extent of evidence on pharmacokinetics of centchroman among both non-lactating and breastfeeding women.

METHODS

A protocol for this scoping review was developed a priori using the Arksey and O'Malley York's five-stage framework.¹³ The five steps of the scoping review were: (1) identifying the research question; (2) identifying the search strategy; (3) study selection; (4) data charting; and (5) collating, summarising and reporting the results.

Step 1: identification of the research question

This scoping review was conducted to answer the following primary research question: *What is the current state of evidence on effectiveness and side effects of centchroman as a contraceptive pill (weekly pill and postcoital pill)?* The secondary research questions were: *What is current available evidence on mechanism of action of centchroman in women?*

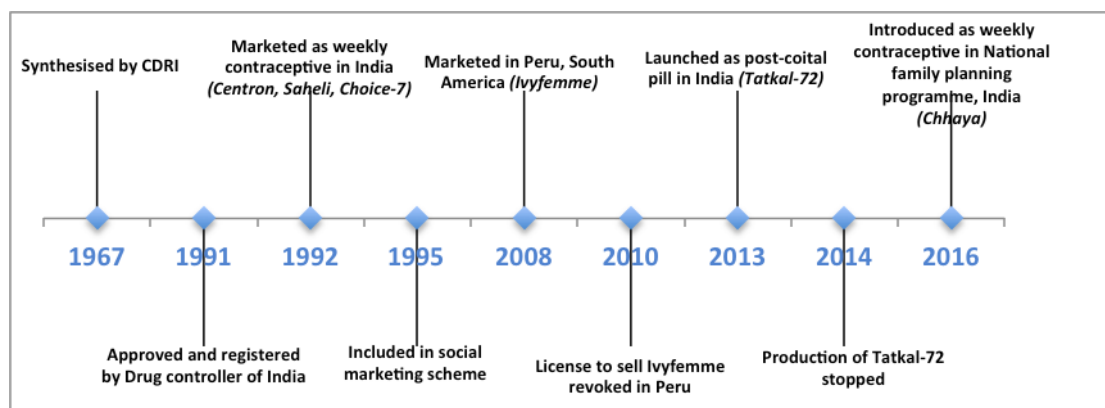


Figure 1 Key milestones on evolution of centchroman. CDRI, Central Drug Research Institute.

What is current evidence on pharmacokinetics of centchroman in breastfeeding women and non-lactating women?

Step 2: identification of relevant studies (search strategy)

To address the research questions, we developed a detailed search strategy to identify all relevant publications on centchroman. The following Medical Education Subject Headings terms were identified and used: centchroman, ormeloxifene, saheh, safety, pharmacokinetics, effectiveness, efficacy and mechanism of action. Using the search terms, we systematically searched the following electronic databases for studies published from 1970 up to 27 July 2017: MEDLINE, EMBASE, INDMED, Cochrane Library and Google Scholar. The search was most recently rerun on 23 January 2019 (no new studies added).

No limits were placed on the searches. An example of the search strategy in EMBASE is given as follows: “centchroman/exp OR ‘1 [2 [4 (7 methoxy 2, 2 dimethyl 3 phenylchroman 4 yl) phenoxy] ethyl] pyrrolidine’:ti,ab,de OR ‘2, 2 dimethyl 3 phenyl 4 [4 (2 pyrrolidinoethoxy) phenyl] 7 methoxychroman’:ti,ab,de OR ‘3, 4 trans 2, 2 dimethyl 3 phenyl 4 [4 (2 pyrrolidinoethoxy) phenyl] 7 methoxychroman’:ti,ab,de OR ‘7 methoxy 2, 2 dimethyl 3 phenyl 4 [4 (2 pyrrolidin 1 ylethoxy) phenyl] chroman’:ti,ab,de OR ‘centron’:ti,ab,de OR ‘choice 7’:ti,ab,de OR ‘levormeloxifene’:ti,ab,de OR ‘ormeloxifene’:ti,ab,de OR ‘saheh’:ti,ab,de OR ‘saheli’:ti,ab,de OR ‘shaeli’:ti,ab,de OR ‘trans 2, 2 dimethyl 3 phenyl 4 [4 (2 pyrrolidinoethoxy) phenyl] 7 methoxychroman’:ti,ab,de OR ‘centchroman’:ti,ab,de OR ‘31477-60-8’:rn”.

Furthermore, websites such as CDRI, Indian Council of Medical Research (ICMR), Clinical Trials Registry-India, WHO and Popline were searched for studies and scientific reports on centchroman. We searched websites of two major drug authorities, Food and Drug Administration and European Medicines Agency, and found no information on the relationship of ormeloxifene/centchroman and oral contraceptives were available on these websites. In addition, we searched for conference proceedings, and student master’s and PhD thesis. The reference lists of all the retrieved studies were searched to identify any additional studies of relevance. We contacted authors to provide studies and additional information that was unavailable.

Step 3: selection of studies for review

We included studies from 1970 to present (2019), to reflect the period during which centchroman was first synthesised and drug trials initiated. No limits were placed on language and location of study. We included studies on women using centchroman only as a contraceptive pill (weekly pill or emergency postcoital pill). Table 1 depicts the eligibility criteria.

After running the search, all the retrieved studies were exported into EndNote X7 reference management software. The EndNote program was used to check for duplication. The study selection process consisted of two levels of screening:

1. *Title and abstract review:* Two reviewers (RK, KPA) independently screened the title and abstract of all the retrieved citations for inclusion guided by the eligibility criteria. An article that was considered relevant by either or both the reviewers was included for full-text review, and any discrepancies were resolved through discussion. Full-text articles that were excluded at the screening stage had reasons for exclusions documented.
2. *Full-text review:* In the second step, the reviewers (RK, KPA) independently assessed the full-text articles to determine if they met the inclusion and exclusion criteria. Any disagreement was resolved by mutual discussions between the reviewers. For included studies, two authors (RK, KPA) extracted the data using the data-charting sheet.

Step 4: charting the data

A data-charting sheet was designed in Microsoft Excel to extract the general characteristics of each study. Information retrieved included study characteristics (authors, country, region, year published, study aim, study design, number of participants) and key research topics (side effects, effectiveness, mechanism of action or pharmacokinetics of centchroman). For each research topic separate data-charting sheets were used to extract relevant information from each included study. The data-charting sheets were constantly updated through the review process.

Table 1 Inclusion/exclusion criteria

Criteria	Inclusion	Exclusion
Study design	Quantitative, qualitative and mixed methods study, systematic review	Studies on animals, narrative review
Location	Any country	None
Date	1970 to present (2019)	Before 1970
Language	All languages	None
Research focus	Main focus on safety, side effects, effectiveness, mechanism of action and pharmacokinetics when used as a contraceptive	Main focus on non-contraceptive uses of centchroman
Document type	Case reports, scientific reports, primary research article, systematic reviews, commentaries, letter to editors, conference proceedings, master’s and PhD thesis	Narrative reviews, newspaper and magazine articles

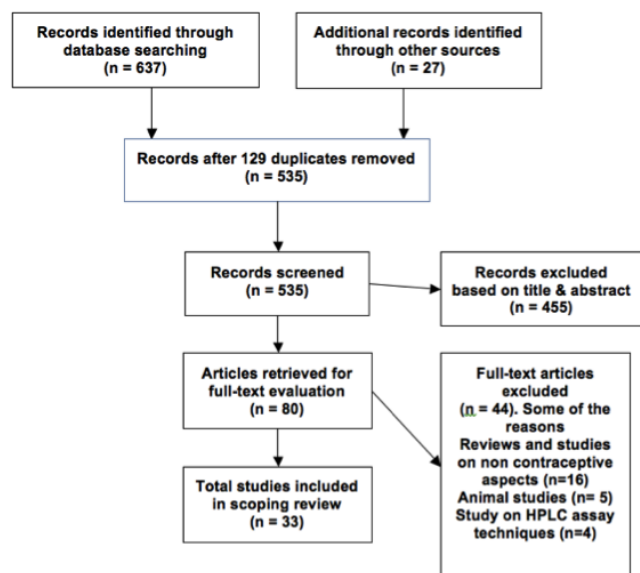


Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. HPLC, high-performance liquid chromatography.

Step 5: collating, summarising and reporting the results

To summarise the findings for this scoping review, each author repeatedly reviewed the extracted evidence independently. The extracted data were summarised based on the individual research questions and around the following outcomes: effectiveness and side effects when used as a weekly or postcoital contraceptive pill, and mechanism of action as contraceptive pill in women and pharmacokinetics of centchroman in non-lactating women and in breastfeeding women. The data extracted from the data-charting sheet were analysed descriptively (frequencies and percentages) to facilitate categorisation, charting and discussion. Scoping reviews aimed to identify, map findings and to provide an overview of the available literature in the topic area rather than an assessment of study quality.¹⁴

Patient and public involvement

Patients and public were not involved in this review.

RESULTS

Of the 664 articles initially identified by our search criteria, only 33 met the inclusion criteria for this scoping review (figure 2). Of these 33 studies, 21 (64%) were experimental (20 non-randomised clinical trials and 1 randomised controlled trial (RCT)), 4 (12%) were observational (descriptive studies), 3 (9%) were case reports, 3 (9%) were national guidelines and 2 (6%) were annual reports.

We identified 8 studies on effectiveness of centchroman as a weekly contraceptive pill, 1 study on effectiveness of centchroman as a postcoital pill, 13 studies on side effects of centchroman (weekly and postcoital pill), 2 on mechanism of action in women and 12 studies on pharmacokinetics among non-lactating and breastfeeding women.

All studies were conducted in India and reported in English. The earliest study was published in 1976 and the latest in 2017. The full texts of studies were available for all except one study for which only the abstract was available.¹⁵ Research publications on centchroman have increased in frequency in the recent years with 39.4% of studies published in the last 10 years (2007–2017) and 60.6% in the previous 30-year period (1976–2006). Roughly half (54.5%) of the studies were published from the developers of the pill (CDRI), and all were clinical trials. The general characteristics of the included studies are detailed in table 2.

Mechanism of action of centchroman

Two clinical trials in our review report the mechanism of action of centchroman among women.^{16 17} The first study was conducted among eight women with ovulatory failure. The women were non-randomly allocated into one of three treatment arms, where centchroman was administered in doses of 15, 30 or 60 mg daily for 10–20 days.¹⁶ Increased levels of plasma progesterone, urinary pregnanediol and oestrogen were observed reflecting that centchroman stimulates the pituitary ovarian axis. The authors concluded that centchroman could induce ovulation in anovulatory women. The second study was conducted among 10 healthy women, non-randomly allocated into two groups. Six women received 120 mg/week and four women received 60 mg/week schedule for 2 months. Increase in cycle length was noticed in all cases probably due to lengthening of the follicular phase. The authors concluded that centchroman at the mentioned doses does not seem to inhibit ovulation although it may delay it; it exerts its contraceptive effect mainly due to its action on cervical mucus and endometrial affecting sperm transport and implantation.¹⁷

Animal studies demonstrated that centchroman acts by increasing the speed of transport of the zygote through the fallopian tubes, so that it reaches the uterus early. Second, it accelerates blastocyst formation, so that it is hypermature when it reaches the endometrium and fails to implant. Lastly, it acts by inhibiting endometrial receptivity to blastocyst signals and by suppressing endometrial proliferation and defective endometrial decidualisation, so that it is not adequately prepared to receive a fertilised egg when it reaches the uterus.^{2 4 6 18}

Pharmacokinetics of centchroman

In non-lactating women

Five clinical trials conducted by CDRI report the pharmacokinetics of centchroman in non-lactating women.^{15 19–22} Of these, two trials report pharmacokinetics after administration of single 30 mg dose of centchroman,^{20 21} blood samples were collected at regular intervals up to 672 hours after drug administration in both, one trial reported pharmacokinetics following administration of single 60 mg dose, blood samples were collected at regular intervals up to 504 hours after drug administration¹⁹ and one trial described pharmacokinetics after

Table 2 General characteristics of included studies

Study No	Study design	Author/year	Sample size	Purpose	Outcome
1	Clinical trials	Roy <i>et al</i> * (1976) ¹⁶	8	To study the ovulation inducing action of centchroman in anovulatory women	Mechanism of action
2		Chandra <i>et al</i> * (1977) ³⁹	A. 40 B. 28	To determine the maximum tolerated dose of centchroman in human volunteers and to find out any toxic effects the study was carried out in two parts: (A) single-dose study and (B) multiple-dose study	Side effects
3		Vaidya <i>et al</i> * (1977) ¹⁷	10	To evaluate various clinical and hormonal parameters during immediate pretherapy and the first therapy cycle for evaluating its effect on hypothalamic-pituitary-ovarian axis	Mechanism of action, side effects
4		Srivastava <i>et al</i> * (1984) ²⁵	-	To study the binding of centchroman to steroid-binding proteins in human plasma	Pharmacokinetics
5		Nityanand and Singh* (1988) ³²	A. Until November 1986: 648 April 1987 to November 1988: 100	To determine the contraceptive efficacy of centchroman in a multicentric trial of centchroman with 30 mg weekly dose. The study reports results in two parts: (A) phase III clinical trial until November 1986 and (B) extended phase III trials (April 1987 to November 1988).	Effectiveness (weekly), side effects
6		Puri <i>et al</i> * (1988) ³³	467	To determine the contraceptive efficacy of centchroman in a multicentric trial in a 30 mg weekly dose. This paper reports results up to June 1984.	Effectiveness (weekly), side effects
7		Paliwal <i>et al</i> * (1989) ¹⁹	2	To determine pharmacokinetics after a 60 mg oral dose of centchroman in normal healthy women	Pharmacokinetics
8		Nityanand and Kamboj* (1994) ²³	377	(A) To study the efficacy of centchroman in a biweekly-cum-weekly mode of administration (B) To establish the safety of this dosage schedule by serial ultrasounds	Effectiveness (weekly), side effects
9		Paliwal <i>et al</i> * (1994) ²⁷	3	To determine pharmacokinetics of centchroman in serum and breast milk among three nursing women	Pharmacokinetics
10		Gupta <i>et al</i> * (1995) ²⁸	13	To assess peak and trough levels of centchroman in breast milk and serum after a single 30 mg dose and after a 30 mg twice-a-week dose for 12 weeks and to calculate quantity ingested by infants	Pharmacokinetics
11		Lal <i>et al</i> * (1995) ²⁰	11	To determine pharmacokinetics of centchroman after a single 30 mg dose in healthy women	Pharmacokinetics
12		Nityanand <i>et al</i> * (1995) ²⁹	A. 277 B. 573	(A) To study the effect of centchroman on ovaries, (B) to determine reversibility and effect on progeny among centchroman users, (C) to study whether it is safe to administer centchroman to lactating women	Pharmacokinetics
13		Gupta <i>et al</i> * (1996) ³⁰	4	To assess pharmacokinetics of centchroman in maternal serum and breast milk in nursing women after a single 30 mg tablet of centchroman	Pharmacokinetics
14		Lal <i>et al</i> * (1996) ²¹	6	To compare the bioavailability of two pharmaceutically equivalent brands of centchroman tablets: Saheli versus Centron (double-blind cross-over study)	Pharmacokinetics
15		Lal <i>et al</i> * (1998) ¹⁵	3	To study the pharmacokinetic profile following the recommended dosage profile in normal healthy women	Pharmacokinetics
16		Khurana <i>et al</i> * (1999) ²⁶	2	To determine the extent of protein binding of centchroman at 1 and 10/ mL concentration in drug-free human serum samples	Pharmacokinetics
17		Lal <i>et al</i> * (2001) ²²	60	To assess the pharmacokinetic parameters of centchroman with dosing schedule of single 60 mg loading dose, followed by 30 mg weekly doses. To assess steady-state minimum concentration of centchroman after six different 30 mg dosing schedules.	Pharmacokinetics
18		Khurana <i>et al</i> * (2002) ²⁴	17	To evaluate the tissue/serum ratio of centchroman in uterus at the maximum drug concentration	Pharmacokinetics
19		ICMR (2009–2010) ³⁴	720 (439 centchroman and 381 for Cu-T)	Phase IV multicentric study to evaluate the efficacy and side effects of centchroman	Effectiveness (weekly)
20		ICMR (2010–2011) ³⁵	2087 (934 with centchroman and 1153 with Cu-T)	Update of the phase IV multicentric study on centchroman	Effectiveness (weekly)

Continued

Table 2 Continued

Study No	Study design	Author/year	Sample size	Purpose	Outcome
21	RCT	Mittal <i>et al</i> (2009) ³¹	150	To investigate the use of centchroman as an effective method of emergency contraception and to compare its efficacy and side effects with single and double doses of levonorgestrel regimen	Effectiveness (postcoital pill), side effects
22	Descriptive study	Tandon (1982) ³⁶	17	To study the effect of centchroman on biochemical profile, ovulation and ovarian size (duration: 12 months)	Effectiveness (weekly), side effects
23		Ghosh (2014) ³⁷	27	To assess the pattern of usage of contraceptive pill/oral contraceptives in a hospital setting (duration: 8 months)	Effectiveness (weekly), side effects
24		Nair and Jayasimhan (2016) ³⁸	153	To study the effectiveness of centchroman as contraceptive, to study possible causes of centchroman failure and to study incidence of side effects of centchroman (duration: 12 months)	Effectiveness (weekly), side effects
25		Agrawal <i>et al</i> (2016) ⁴⁰	25	To study the adverse drug reactions of centchroman used for contraceptive purpose (duration: 12 months)	Side effects
26	Case report	Malhotra <i>et al</i> (2011) ⁴¹	1	Case of young women using centchroman for a long duration in an unsupervised fashion, presenting with menorrhagia	Side effects
27		Agarwal <i>et al</i> (2014) ⁴²	1	Case of a woman using centchroman for 10 years in an unsupervised manner, presenting with abnormal uterine bleeding and enlarged uterus	Side effects
28		Padmaja <i>et al</i> (2013) ⁴³	1	Case of an unmarried 18-year-old woman on unsupervised 60 mg centchroman twice weekly (for menorrhagia) for 2 years, presents with c/o excess menstrual flow	Side effects
29	National guideline/reference manual	MoHFW, Government of India (2016) ⁴	–	Reference manual for contraceptive pill/oral contraceptives	Dosage schedule, side effects
30		MoHFW, Government of India (2017) ⁴⁴	–	Guidelines on contraceptives: an update on new family planning methods for ASHA workers	Dosage schedule, benefits and side effects
31		MoHFW, Government of India (2005) ⁴⁵	–	Contraceptive updates – reference manual for doctors on doses, advantages and side effects. The Government of India has planned to organise series of 'contraception updates' seminars for doctors in public and private healthcare sectors, to help standardise delivery of information.	Mechanism of action, side effects
32	Annual report	Population Foundation of India (2014) ²	–	Report on spacing methods for family planning	Mechanism of action, effectiveness, side effects and advantages
33		CSIR-Central Drug Research Institute (2017) ¹⁸	–	Annual report of CSIR, which includes unique features of centchroman and details of its inclusion in the national family planning programme, India	Unique features and details of its inclusion in national FP programme

ASHA, Accredited Social Health Activist; CSIR, Council of Scientific and Industrial Research; FP, family planning; ICMR, Indian Council of Medical Research; MoHFW, Ministry of Health and Family Welfare; RCT, randomised controlled trial.

60 mg loading dose followed by 30 mg weekly dose.²² In addition, one trial reported pharmacokinetics following administration of 30 mg biweekly for 12 weeks (only study abstract available).¹⁵

The peak serum concentration (C_{\max}) of centchroman was reported by three of these studies.^{15,20,22} C_{\max} following a 30 mg dose is nearly half ($55.5 \pm 14.5 \mu\text{g/L}$) of that observed with a 60 mg dose, indicating C_{\max} is dose dependent.²⁰ The time taken to reach the peak (T_{\max}) following 30 or 60 mg dose was between 4 and 8 hours. In the multiple dose study, it was noted that C_{\max} was the same after a single 30 mg dose ($55 \pm 14.2 \text{ ng/mL}$) and repeated dosing did not alter the C_{\max} ($62.4 \pm 11.9 \text{ ng/mL}$) or T_{\max} (6 hours).¹⁵ This indicated that there was no accumulation of centchroman in the body with repeated doses.

The steady-state minimum concentration of centchroman (C_{\min}) was reported in two studies.^{22,23} The C_{\min} following single 30 mg dose was 16 ng/mL and it was almost twice following 30 mg twice-weekly dose at 28 ng/mL , indicating it is dose dependent. The C_{\min} at 336 hours ($25.2 \pm 12.4 \text{ ng/mL}$) was similar to C_{\min} at day 80 ($24.2 \pm 4.8 \text{ ng/mL}$), showing the steady-state concentration of the drug was achieved at fifth 30 mg dose.¹⁵

Centchroman is widely distributed in the body due to its high-lipid solubility. The volume of distribution and drug clearance following a 30 mg (V_d/F : $1328 \pm 458 \text{ L}$, Cl/F : $6.35 \pm 1.8 \text{ L/hour}$) or a 60 mg dose (V_d/F : 1077 L ; 1909 L , Cl/F : 4.4 ; 7.6 L/hour) are comparable, suggesting that they are dose independent.^{19,20} One study on the distribution of centchroman in the endometrium, following a 30 mg single dose, reports that centchroman is rapidly absorbed and distributed to the endometrium and at any given time, the concentration of centchroman in the uterus (mean: $152 \pm 39 \text{ ng/g}$) is 1.93 times higher than the corresponding levels in the serum (mean: $55 \pm 13 \mu\text{g/L}$).²⁴

Two clinical trials report the binding of centchroman to plasma proteins.^{25,26} These show that centchroman binds strongly to serum albumin in healthy women. It has a low-affinity, high-capacity binding with a dissociation (K_d) rate constant of $13.19 \times 10^{-6} \text{ M}$. The binding increases with an increase in protein content. The trial by Khurana *et al* showed that with a method that includes dilution of serum, protein binding is found to be 95.2 ± 1.1 and $88.2\% \pm 2.1\%$ at 1 and $10 \mu\text{g/mL}$. While in method II, which is devoid of any dilution, protein-binding estimates were higher at 101.8 ± 1.3 and $94.9\% \pm 3.6\%$ at 1 and $10 \mu\text{g/mL}$.²⁶

Centchroman is metabolised in the liver into active and inactive metabolites; the active metabolite (7-desmethyl centchroman) is responsible for anti-implantation effect.²²

In breastfeeding women

Four clinical trials report pharmacokinetics of centchroman in breastfeeding women.^{27–30} These studies report the infant is exposed to a small percentage (2.5%–9.5%) of the maternal dose of centchroman through breast milk. The C_{\max} in breast milk was higher ($70.7 \pm 27.5 \mu\text{g/L}$) than C_{\max} in the serum ($60.7 \pm 12.2 \mu\text{g/L}$), and the T_{\max}

was attained later in the milk (8.50 ± 1.7 hours) than in the serum (6 hours).³⁰

Centchroman as postcoital contraceptive pill

One RCT among 150 women reports the effectiveness of centchroman as postcoital pill within 120 hours of single unprotected intercourse.³¹ The aim of this trial was to compare the efficacy and side effects of two different centchroman regimens with 1.5 mg single-dose levonorgestrel. In this trial, women were randomly allocated into three groups (50 women in each group). Women in group I received a 1.5 mg single dose of levonorgestrel tablet, single 60 mg dose for group II, and group III received one 30 mg tablet, twice a day, at an interval of 12 hours. The side effects reported from groups I, II and III were menstrual delay >7 days (6%, 6.2%, 2%), headache (8%, 10.6%, 14.3%), abdominal pain (2%, 6.3%, 8.2%) and nausea (14%, 4.3%, 4%), respectively, and 10% in group I reported dizziness. Four per cent in group I, 2% users in group II and 6% users in group III reported pregnancies, all classified as method failure (MF) (effectiveness 96%, 98%, 94%). This trial concluded that single-dose centchroman regimen (group II) is well compared with single-dose regimen of levonorgestrel both in terms of efficacy and safety.

Effectiveness of centchroman as a weekly contraceptive

Eight studies (five clinical trials and three observational studies) included in the scoping review report the effectiveness of centchroman^{23,32–38} (table 3). Effectiveness in the included studies was calculated from the number of pregnancies from MF. Any pregnancy associated with non-compliance of the drug is classified as user failure (UF).

Clinical trials

Four of these studies report the results from the phase III and phase IV trials on centchroman. The first study is a multicentric phase III clinical trial (until June 1984), conducted among 467 women across 10 family welfare centres.³³ Centchroman was administered as a 30 mg once-a-week tablet starting on the first day of the menses, and thereafter one tablet was taken on the same day every subsequent week. An additional tablet had to be taken on the first day of every subsequent menstrual cycle irrespective of the weekly tablet. Women had regular check-ups every month. The duration of centchroman use in this trial ranged from 1 to 36 months. A total of 19 MF and 44 UF pregnancies occurred during the study duration (95.9% effective). Of the 19 MF pregnancies, 14 (73.7%) occurred in the first 6 months of centchroman use and only 1 (5.3%) after 1 year of drug use (Pearl Index 4.2). The 44 UF pregnancies occurred because the women did not adhere to the pill schedule, with 20 pregnancies (45.5%) occurring in the first 6 months, 15 pregnancies (34%) between 7 and 12 months and 9 pregnancies (20.5%) after 1 year of pill use.

The second study is an extension of the phase III multicentric clinical trial, and reports the results in two parts:

**Table 3** Summary of studies on effectiveness of centchroman as a weekly contraceptive pill

Ref*	Dosage	Sample size	Pearl Index	Method failure	User failure	Effectiveness
Clinical trials						
33	30 mg once a week. First tablet on first day of menses and thereafter one tablet on that day every week.	467	4.2	19 (4.1%)	44 (9.4%)	95.9%
32	One additional tablet was taken on first day of every subsequent menses irrespective of weekly tablet (phase III).	648	3.7	27 (4.2%)	66 (10.2%)	95.8%
23	30 mg twice a week for 3 months, followed by 30 mg once a week	100	1.2	–	–	–
34 35	30 mg twice a week for 3 months, followed by 30 mg once a week	377	1.83	6 (1.6%)	24 (6.7%)	98.4%
34 35	30 mg twice a week for 3 months, followed by 30 mg once a week	755 (out of 934)	n.a.	20 (2.6%)	–	97.4%
Observational studies						
38	30 mg twice a week for 3 months, followed by 30 mg once a week	153	2	7 (4.6%)	4 (2.6%)	95.4%
36		17	0	0	0	100%
37		27	n.a.	Ineffective in two users (7%)		93%

*The complete study titles are in the reference section.
n.a., not applicable.

(A) phase III trial until November 1986 and (B) extended phase III clinical trial (April 1987 to November 1988).³² In the study (until 1986), 648 women were recruited from 10 family welfare centres. The dosage schedule of centchroman was same as the phase III trial.³³ The duration of pill use ranged from 1 to 52 months. Twenty-seven MF and 66 UF pregnancies occurred in the study duration (95.8% effective)/Pearl Index of 3.7. Among the 27 MF pregnancies, 19 (70%) occurred in the first 5 months and 4 (15%) occurred after 1 year of centchroman use. For the extended phase (April 1987 to November 1988), 100 women were recruited in five additional centres. The details of number of pregnancies in the extended phase are unavailable, however Pearl Index is reported as 1.2.

Phase IV clinical trial (postmarketing trial) was initiated in 2009, across 18 human reproductive research centres of ICMR, India.^{34 35} It was a non-randomised clinical trial, with Cu-T users being the comparison group. The dosage schedule for phase IV was 30 mg centchroman twice a week for 12 weeks, followed by once-weekly 30 mg thereafter. The trial enrolled 2087 women (934 with centchroman and 1153 with Cu-T). The interim results of this phase (on 755 centchroman users) reveal 20 MF pregnancies (97.4% effective). The detailed results of this phase are neither published nor available on request.

One conference paper²³ reports a clinical trial among 377 women to study the effectiveness of centchroman using the schedule: 30 mg centchroman twice a week for 12 weeks followed by 30 mg once a week. The study duration ranged from 1 to 27 months. Six MF and 24 UF pregnancies were reported during the study duration (effectiveness: 98.4%). Of the six MF, 2 (33%) failures

occurred during the first month, 2 (33%) at 3 months and 1 (17%) each at 9 and 15 months.

Observational studies

Additionally, three observational studies report effectiveness of centchroman ranging from 93% to 100% (table 3). In the first study, 153 women were followed up for 12 months, of which 11 women became pregnant (4.6% MF and 2.6% UF). Majority (81%) of pregnancies occurred during the first 6 months while all occurred within 9 months of initiation of the pill.³⁸

In the second study, 27 women were followed up for 8 months; effectiveness was 93%.³⁷ The authors did not report details of MF or UF. In the third study, 17 women were followed for 12 months; effectiveness was 100%.³⁶

SIDE EFFECTS OF CENTCHROMAN USE

Thirteen studies^{17 23 31–33 36–43} report side effects from centchroman use as a weekly contraceptive pill (tables 4 and 5). We are reporting frequently reported side effects under the following headings: menstrual irregularities, other side effects and changes on ultrasound examination.

Menstrual irregularities

The most frequent side effect among centchroman users is menstrual irregularities like: short cycles lasting <20 days (reported by four studies; 4%, 5%, 3%, 8% users),^{23 32 33 40} prolonged cycles >45 days (six studies; 8.8%, 10%, 10%, 3%, 3.7%, 26%, 16% users) [^{20 23 33 36 38 40} scanty bleeding lasting 1 or 2 days (two studies; 12%, 36.7% users)^{36 38} and menstrual delay >30 days (one study; 15% users).⁴⁰ Five studies report continuous bleeding as a side effect. Of

Table 4 Summary of studies on other side effects with centchroman use (percentage of women with the side effects)

Ref*	Sample size	Duration of use (dosage)	Nausea/vomiting (%)	Headache (%)	Backache (%)	Giddiness (%)	Abdominal pain (%)	Fever (%)	Low haemoglobin (%)	Breast tenderness (%)
39	23	Phase I trial: single dose of dose ranging from 5 to 320mg	+	+	-	+	-	-	-	-
	28	30 days (either 60 or 120 mg)	-	+(10.7%)	+(7.1%)	+(7.1%)	-	+(7.1%)	-	-
41	1	7 years (30mg weekly once)	-	-	-	-	-	-	+	-
31	Group 1: 49 Group 2: 47	Single dose (group 1: 60mg, group 2: 30mg two tabs taken 12 hours apart)	Group 1: (4.3%) Group 2: (4%)	Group 1: (10.6%) Group 2: (14.3%)	-	-	Group 1: (6.3%); Group 2: (8.2%)	-	-	Group 2: (2%)
17	Group A: 6 Group B: 4	2 months (group A: 120mg/week, group B: 60mg/week)	-	-	-	-	-	-	-	-
42	1	10 years (30mg)	-	-	-	-	-	-	+	-
38	153	100%–3 months, 97%–6 months, 93%–9 months, 85%–12 months (30mg twice weekly for 3 months followed by weekly 30mg)	+(0.7%)	+(0.7%)	-	+(1.3%)	-	-	-	-
40	25	12 months (30mg twice weekly for 3 months followed by weekly 30mg)	-	-	-	+	-	-	-	-
						At 3 months: (8%) At 6 months: (12%)				
43	1	24 months (60mg twice weekly for 3 months followed by weekly 30mg)	-	-	-	-	-	-	+	-
37	27	1–6 months: 18, 7–12 months: 6, >12 months: 3 (30mg twice weekly for 3 months followed by weekly 30mg)	-	+(3.7%)	-	+(3.7%)	+	-	+(11%)	-
36	17	12 months (30mg twice weekly for 3 months followed by weekly 30mg)	-	-	-	-	-	-	-	-
33	467	30mg once a week (phase III multicentric trial up until June 1984)	+(0.2%)	-	-	-	-	+(0.4%)	-	-
32	648	A. 30mg once a week (phase III multicentric trial until November 1986) B. Extended phase III trial (April 1987 to November 1988)	+(0.2%)	+(0.8%)	-	+(0.8%)	-	-	-	-
23	377	30mg twice a week for 3 months, followed by 30mg once a week	-	-	-	-	-	-	-	-

+ indicates yes and – indicates no.

*The complete study titles are in the reference section.

Table 5 Summary of studies on menstrual irregularities with centchroman use

Ref*	Dosage of centchroman	Sample size	Short cycle ≤20 days	Prolonged cycle >45 days	Scanty bleeding (1 or 2 days)	Amenorrhea	Menstrual delay >7 days	Menstrual delay >15 days	Menstrual delay >30 days	Continuous bleeding
39	Phase I trial: 60 mg—10 women, 120 mg—8 women, placebo—10 women	28	60 mg: 10% 120 mg: 12.5%	—	—	—	—	60 mg: 10%	120 mg: 12.5%	—
41	30 mg once per week	1	—	—	—	—	—	—	—	100%; duration 20 days
31	Group 1: single 60 mg Group 2: two doses of 30 mg 12 hours apart	150	—	—	—	—	Group 1: 6.3% Group 2: 2%	—	—	—
17	Group A: 120 mg/week Group B: 60 mg/week	10 (A: 6, B: 4)	—	—	—	—	Group A: 50% Group B: 25%	—	—	—
42	Unsupervised and irregular dose (30 mg)	1	—	—	—	—	—	—	—	100%; duration 45 days
38	30 mg twice a week for 3 months, followed by 30 mg once a week	153	—	26%	12%	7%	—	—	—	0.6%
40	30 mg twice a week for 3 months, followed by 30 mg once a week	25	8%	16%	—	—	—	—	16%	—
43	60 mg twice weekly for 3 months followed by once weekly for the next 3 months	1	—	—	—	—	—	—	—	100%, duration 10 days
37	30 mg twice a week for 3 months, followed by 30 mg once a week	27	4 women with menstrual irregularities (14.8%)	—	—	—	—	—	—	—
36	30 mg twice a week for 3 months, followed by 30 mg once a week	17	—	3%	37.6%	—	—	—	—	1%
33	30 mg once a week (phase III multicentric trial up until June 1984)	467	5%	10%	—	—	—	—	—	—
32	A. 30 mg once a week (phase III multicentric trial until November 1986) B. Extended phase III trial (April 1987 to November 1988)	648 100	4.21% 4%	8.84% 10%	—	—	—	—	—	—
23	30 mg twice a week for 3 months, followed by 30 mg once a week	377	2.7%	3.7%	—	—	—	—	—	—

*The complete study titles are in the reference section.

these, three are case reports of women on unsupervised long-term use of the pill, presenting with continuous bleeding of 10–45 days' duration.^{41–43} Two other studies report continuous bleeding among 1% of centchroman users.^{36 38} The Indian national guidelines on oral contraceptive use report menstrual delay among 8% of centchroman users, and state it typically occurs in the first 3 months of centchroman use.⁴

Other side effects

The phase I trial on centchroman initiated in 1970s included 51 participants (23 females and 28 males).³⁹ At the end of this phase, it was concluded that a dose of 5–320 mg centchroman is well tolerated by humans, because it did not show any major side effect or any abnormality in laboratory parameters.

Phase III multicentric trials (until 1984) reported one woman with 8 kg weight gain over 34 months' period of drug use, one of loose stools, vomiting, and two with fever.³³ In the phase III trial (until 1986), five women complained of giddiness, five of headache, one of anorexia, one of loose motions and vomiting and one ectopic pregnancy.³²

The other side effects reported from included studies were: headache (two studies; 1% and 4% users),^{37 38} giddiness (two studies; 1.3% and 12%),^{37 38} nausea (one study,

0.7%)³⁸ and giddiness with abdominal pain (one study; 8% at 3 months and 12% users at 6 months).⁴⁰ In addition, three case reports provide detail on women with complaints of continuous bleeding and on investigation are found to be severely anaemic (Hb: 4 g/dL, 5 g/dL and 7 g/dL).^{41–43} Further, an observational study reported anaemia in 11% users.³⁷

Changes in the ovaries and uterus

Seven studies^{29 35 36 38 41–43} in the review report the ultrasound findings among centchroman users (table 6). The main findings reported by these studies are: (A) three case reports found a bulky uterus with distorted endometrial cavity,^{41–43} and (B) one study found ovarian enlargement among 18% of the users.³⁸ In another study among the 175 women who were followed up for 40 months on centchroman, 15% showed ovarian enlargement. The enlargement was unilateral, transient and never persisted and got resolved despite centchroman therapy.²⁹ One study among 17 women, however, showed no changes in ovaries.³⁶ The preliminary results of the phase IV trial report four women with ovarian cysts <5 cm and two women with cysts >5 cm.³⁵

Table 6 Summary of studies on ultrasound findings among centchroman users

Ref*	Women who underwent USG (n)	Dosage of centchroman	Duration of centchroman intake	Ultrasound findings
41	1	30 mg once a week	7 years	▶ Enlarged uterus with well-delineated endometrial thickness and a mixed echogenic collection in a distorted endometrial cavity
42	1	30 mg once a week (irregular and unsupervised)	10 years	▶ Mixed echogenic collection in a distorted endometrial cavity of a bulky uterus (101×84 mm) ▶ Ovaries were normal.
38	28 (of 153 participants)	30 mg twice weekly for 3 months, followed by 30 mg once weekly	3–12 months	▶ 20 women had normal-looking ovaries. ▶ 4 (14.2%) women had follicular cysts. ▶ 4 (14.2%) women had corpus luteal cysts. ▶ No cyst was bigger than 2.5–3 cm.
43	1	60 mg twice weekly for 3 months, followed by once weekly (unsupervised use)	2 years	▶ Bulky uterus with 8×4 cm hyperechoic area with increased AV channels within it ▶ Endometrium was not separately made out.
36	17	30 mg twice weekly for 3 months, followed by 30 mg once weekly	12 months	▶ No significant ovarian enlargement was detected during centchroman use.
23	64 (of 377 participants)	30 mg twice a week for 3 months, followed by 30 mg once a week	12–30 months	▶ Two cases of enlarged ovaries ▶ One showed enlarged ovary at 6 months and one at 12 months. ▶ In both cases, enlargement was due to mature unruptured follicle. ▶ On subsequent examination at 12 and 20 months, ovaries were normal.
29	175	30 mg twice a week for 3 months, followed by 30 mg once a week	Up to 40 months	▶ 15% of women had ovarian enlargement. ▶ Enlargement was unilateral and transient.

No additional data are available.

*The complete study titles are in the reference section.

AV channels, Arteriovenous channels; USG, ultrasonography.



DISCUSSION

This is the first scoping review that systematically identified and summarised the studies on centchroman as a contraceptive pill. Our primary aim for this scoping review was to collate the overall evidence available on the current state of knowledge on mechanism of action, pharmacokinetics, side effects and effectiveness of centchroman as a weekly and postcoital contraceptive pill. The methods used throughout the different stages of the review were rigorous, transparent, and the process is documented in sufficient detail to replicate the research approach. In addition, we interviewed a product manager from the pharmaceutical company that manufactures centchroman in India to gain insight on sales and marketing of centchroman. He said that currently centchroman is only marketed in India as a weekly contraceptive pill, though in the past it has been sold as an emergency postcoital pill and was also marketed in South America for a short period. On effectiveness, with perfect use the failure rate of centchroman was 1%–2%, but with typical use the failure rate increases to 6%–7%. We here recognise the potential conflict of interest, as the pharmaceutical manager may be biased in responses to boost his company sales.

This scoping review identified 33 primary research papers, annual reports, theses and national guidelines on centchroman from India published between 1976 and 2019. Only two studies in our review report the mechanism of action of centchroman in women (sample size: 8, 10).^{16 17}

Eight studies report the effectiveness of centchroman as a weekly contraceptive pill involving a total of 2544 women. The reported effectiveness ranged from 96% to 98% in clinical trials and 93% to 100% in observational studies. This review thus suggests that the effectiveness of centchroman as a weekly contraceptive is slightly lower than what is noted as 98%–99% in the Indian national guidelines.⁴ Only one RCT among 150 women reports the effectiveness of centchroman as a postcoital pill.³¹ It was 98% effective when taken as a single 60 mg within 120 hours of unprotected intercourse. The detailed results of phase IV trials would provide conclusive information on effectiveness.

Thirteen studies report side effects of centchroman use as an oral contraceptive. Continuous bleeding and prolonged cycles >45 days were the two most commonly reported side effects among centchroman users. The side effects profile is similar to that seen with hormonal contraceptive pills. The studies on side effects are of low quality with small sample size. The largest sample for observational studies was 153 women and maximum follow-up was of 12 months. This limits meaningful conclusions to be drawn. Though the phase IV drug trial included a large sample (934 users), but the detailed results of this phase are not published and were not available on request hence could not be used in the review. To the best of our knowledge there has been no published scientific trial comparing side effects of centchroman to other safe and effective contraceptive pill/oral contraceptives. There is

a need for studies with robust study designs comparing centchroman to other hormonal methods.

The Indian national guidelines⁴ have menstrual delay among 8% of the centchroman users, and do not mention any other side effects. We suggest the guidelines be updated to include other side effects as well, so that the health providers can comprehensively counsel the women on the possible side effects during counselling.

CONCLUSIONS

Our scoping review provides a broad and a comprehensive review of currently available literature on centchroman when used as a contraceptive pill. The review demonstrates that despite evidence on effectiveness of centchroman, more research is needed on side effects and mechanism of action. Insufficient evidence exists on its use as a postcoital contraceptive pill. Robust study designs are needed such as RCT or longitudinal studies to compare effectiveness and safety of centchroman with other short-term modern contraceptives such as combined hormonal oral pills or progesterone only pills contraceptives. It is clear that there are extensive gaps in the literature that warrant further studies, both in Indian and international settings. The uncertainty and diversity of side effects and effectiveness in the studies across India implies a lack of body of evidence to make global recommendations on centchroman, a contraceptive method that is licensed and used in the second most populous country in the world.

Acknowledgements We thank Mr Tomas John Allen, librarian at WHO Geneva, for his assistance in developing a search strategy and running the search for this scoping review. We thank Drs Manisha Malhotra, Bulbul Sood, Saswati das (JHPIEGO) and Shalini Singh (ICMR) for their support in identifying the stakeholders and for their valuable suggestions on the protocol and the initial draft of this scoping review. We also thank all the stakeholders who participated in the interviews and shared their experiences with centchroman use.

Contributors The idea for this publication was conceived by RK and JK. RK and KPA prepared the first draft. MA, CAJ, KM and JK provided significant contributions to the draft. All authors reviewed the draft manuscript and approved the final manuscript for publication.

Funding The UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a cosponsored programme executed by the WHO, funded this work.

Disclaimer The funding sources did not play a role in the study design, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication. The conclusions and opinions expressed here are those of the authors and not necessarily those of the funder.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Komal Preet Allagh <http://orcid.org/0000-0002-6272-2135>

REFERENCES

- 1 Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders. *Med Res Rev* 2010;21:302–47.
- 2 Population Foundation of India. Spacing methods of family planning, 2014. Available: http://populationfoundation.in/files/fileattached/Fileattached-1492415902-Family_Planning_methods_Eng.pdf [Accessed Cited 17th November 2017].
- 3 Kamboj VP, Ray S, Anand N. Centchroman a safe reversible postcoital contraceptive with curative and prophylactic activity in many disorders. *Frontiers in Bioscience* 2018;10:1–14.
- 4 Family planning division. *Ministry of health and family welfare, government of India. reference manual for oral contraceptive pills*. New Delhi: Ministry of Health and Family welfare -Government of India, 2016.
- 5 Balasubramanian D. On conception and contraception: the story of Saheli; the Hindu: 24th June 2017. Available: <https://www.thehindu.com/sci-tech/science/on-conception-and-contraception-the-story-of-saheli/article19140909.ece> [Accessed Cited 28th June 2018].
- 6 Lal J. Clinical pharmacokinetics and interaction of centchroman – a mini review. *Contraception* 2010;81:275–80.
- 7 World Health Organization. *WHO drug information: recommended inn list 34 international nonproprietary names for pharmaceutical substances*. 8(4). Geneva: World Health Organization, 1994.
- 8 Chawla PC. CSIR's novel contraceptive drug- a woman's true Saheli. In: Chawla PC, ed. *CSIR news: progress, promise and prospects*. New Delhi: NISCAR Press, 2010: 60 (15 & 16). 171–2.
- 9 Population Research Institute. News from Latin America. One less weapon against the unborn: the abortion pill gets pulled from market. January 1 2010. Population research Institute. Available: <https://www.pop.org/news-from-latin-america-one-less-weapon-against-the-unborn-the-abortion-pill-gets-pulled-from-the-market/> [Accessed Cited 23rd November 2017].
- 10 HLL Lifecare Limited. Innovating for healthy generations. Annual report 2013-2014. Available: http://www.lifecarehll.com/page/render/reference/Annual_Report [Accessed Cited 20th October 2017].
- 11 CSIR-Central Drug Research Institute. Centchroman. Available: <http://cdri.res.in/centchroman.aspx> [Accessed Cited 20th October 2017].
- 12 Hindustan Latex Family Planning Promotion Trust (HLFPPT). Tatkal-72. Available: <https://hlfppt.org/tatkaal-72-contraceptive-pill/> [Accessed Cited 20th October 2017].
- 13 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005;8:19–32.
- 14 Peters MDJ, Godfrey CM, Khalil H, et al. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc* 2015;13:141–6.
- 15 Lal J, Nityanand S, Asthana OP, et al. Multiple dose pharmacokinetics of centchroman in female volunteers. *Indian J Pharmacol* 1998;30:120.
- 16 Roy S, Lakshmi Kumari G, Madoiya K, et al. Induction of ovulation in the human with centchroman: a preliminary report. *Fertil Steril* 1976;27:1108–10.
- 17 Vaidya R, Joshi U, Meherji P, et al. Activity profile of centchroman in healthy female volunteers. *Indian J Exp Biol* 1977;15:1173–6.
- 18 Central Drug Research Institute, Lucknow. Annual report 2016-17. Available: http://www.cdri.res.in/Annual_Reports/Annual_Report_2016_17.pdf [Accessed Cited 21st October 2017].
- 19 Paliwal JK, Gupta RC, Grover PK, et al. High performance liquid chromatographic (HPLC) determination of centchroman in human serum and application to single-dose pharmacokinetics. *Pharm Res* 1989;06:1048–51.
- 20 Lal J, Asthana OP, Nityanand S, et al. Pharmacokinetics of centchroman in healthy female subjects after oral administration. *Contraception* 1995;52:297–300.
- 21 Lal J, Nityanand S, Asthana OP, et al. Comparative bioavailability of two commercial centchroman tablets in healthy female subjects. *Indian J Pharmacol* 1996;28:32–4.
- 22 Lal J, Nityanand S, Asthana OP, et al. Optimization of contraceptive dosage regimen of Centchroman☆. *Contraception* 2001;63:47–51.
- 23 Nityanand S, Kamboj VP, Chandrawati, et al. Contraceptive efficacy and safety of centchroman with biweekly-cum- weekly schedule. In: Puri CP, VanLook PFA, eds. *Current concepts in fertility regulation and reproduction*. New Delhi: Wiley Eastern Ltd, 1994: 61–8.
- 24 Khurana M, Lal J, Kamboj M, et al. Uptake of centchroman by the human uterus. *Clin Drug Investig* 2002;22:715–8.
- 25 Srivastava AK, Agnihotri A, Kamboj VP. Binding of centchroman—a nonsteroidal antifertility agent to human plasma proteins. *Experientia* 1984;40:465–6.
- 26 Khurana M, Paliwal JK, Kamboj VP, et al. Binding of centchroman with human serum as determined by charcoal adsorption method. *Int J Pharm* 1999;192:109–14.
- 27 Paliwal JK, Grover PK, Asthana OP, et al. Excretion of centchroman in breast milk [letter]. *Br J Clin Pharmacol* 1994;38:485–6.
- 28 Gupta RC, Paliwal JK, Nityanand S, et al. Centchroman: a new non-steroidal oral contraceptive in human milk. *Contraception* 1995;52:301–5.
- 29 Nityanand S, Gupta RC, Kamboj VP. Centchroman: current status as a contraceptive. In: Dawn SC, ed. *Centchroman: current status as a contraceptive. Indian progress in family welfare: clinical research on maternal and child health & contraception*. A Misra Calcutta: Dawn books, 1995: 26–31.
- 30 Gupta RC, Nityanand S, Asthana OP, et al. Pharmacokinetics of centchroman in nursing women and passage into breast milk. *Clin Drug Investig* 1996;11:305–9.
- 31 Mittal S, Sehgal R, Jindal VI, et al. Single dose levonorgestrel and two regimens of centchroman for emergency contraception. *J Turk Ger Gynecol Assoc* 2008;9:132–7.
- 32 Nityanand S, Singh L. Clinical evaluation of centchroman: a new oral contraceptive. Hormone antagonists for fertility regulation. In: Puri CP, VanLook PFA, eds. *Indian Soc Study Reprod Fert*. Bombay, 1988: 223–30.
- 33 Puri V, Kamboj VP, Chandra H. Results of multicentric trial of Centchroman. In: Dhawan BN, ed. *Pharmacology for health in Asia*. New Delhi: Allied Publishers, 1988: 439–47.
- 34 Indian Council of Medical Research (ICMR). Reproductive health: annual report 2009-10. Available: <http://www.icmr.nic.in/annual/2009-10/english/rh.pdf> [Accessed Cited 20th November 2017].
- 35 Indian Council of Medical Research (ICMR). Reproductive health: annual report 2010-11. Available: <http://www.icmr.nic.in/annual/2010-11/English%20Annual%20Report/rh.pdf> [Accessed Cited 20th November 2017].
- 36 Tandon D. Effect of centchroman on biochemical profile, ovulation and ovarian size [Masters of Surgery Thesis]. Bundelkhand University, 1992. <https://ia601601.us.archive.org/16/items/in.ernet.dli.2015.269787/2015.269787.Effect-Of.pdf>
- 37 Ghosh S. Prospective observational study of the pattern of usage of oral contraceptive pills [Masters of Pharmacy thesis], 2014. <http://jadunivdspace.jvu.ac.in/bitstream/123456789/29440/1/Acc.%20No.%20DC%201823.pdf>
- 38 Nair HS, Jayasimhan P. A prospective study of centchroman users with special reference to its contraceptive benefit. *J Evid Based Med Healthcare* 2016;3:5374–80.
- 39 Chandra H, Srimal RC, Kamboj VP, et al. Clinical pharmacology studies with centchroman. *Indian J Exp Biol* 1977;15:1170–2.
- 40 Agrawal P, Kushwa V, Mangal BK. Evaluation of safety profile of centchroman for contraceptive purpose. *Natl J Med Allied Sci* 2016;5:41–4.
- 41 Malhotra KP, Sherpa M, Bhatia A. Centchroman: is unsupervised long-term use warranted? case report. *Eur J Contracept Reprod Health Care* 2011;16:403–6.
- 42 Agarwal R, Radhakrishnan G, Radhika AG, et al. Abnormal uterine bleed- an adverse event of long-term centchroman use? *Indian J Mater Child Health* 2014;16:1–7.
- 43 Padmaja A, Vemulapalli P, Jaya Prada Devi K. Rare case of endometrial hyperplasia following unsupervised prolonged use of Ormiloxifene. *IOSR J Dent Med Sci* 2013;5:55–7.
- 44 Family Planning Division. *Ministry of health and family welfare, government of India. An update on new family planning methods for ASHA*. New Delhi: Ministry of Health and Family welfare -Government of India, 2017.
- 45 Ministry of Health and family welfare, Government of India, United Nations Population Fund. *Contraceptive updates. Reference manual for doctors*. New Delhi: Ministry of Health and Family welfare, 2005.