Pregravid contraceptive use and fecundability: prospective cohort study

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ABSTRACT

OBJECTIVE

To evaluate the association between pregravid use of a variety of contraceptive methods and subsequent fecundability.

DESIGN

Prospective cohort study.

SETTING

Denmark and North America, 2007-19.

PARTICIPANTS

17 954 women who had tried to conceive for up to six menstrual cycles at study entry. At baseline, participants reported their contraceptive histories, and personal, medical, and lifestyle characteristics.

MAIN OUTCOME MEASURES

Pregnancy, determined by bimonthly follow-up questionnaires for up to 12 months.

RESULTS

Approximately 38% (n=6735) of participants had recently used oral contraceptives, 13% (n=2398) had used long acting reversible contraceptive methods, and 31% (n=5497) had used barrier methods. Women who had recently stopped using oral contraceptives, the contraceptive ring, and some long acting reversible contraceptive methods experienced short term delays in return of fertility compared with users of barrier methods. Use of injectable contraceptives was associated with decreased fecundability compared with use of barrier methods (fecundability ratio 0.65; 95% confidence interval 0.47 to 0.89). Users of injectable contraceptives had the longest delay in return of normal fertility (five to eight menstrual cycles), followed by users of patch contraceptives (four cycles), users of oral and ring contraceptives (three cycles), and users of hormonal and copper intrauterine devices and implant contraceptives (two cycles). Lifetime length of use of hormonal contraceptive methods was not associated with fecundability.

CONCLUSIONS

Use of some hormonal contraceptive methods was associated with delays in return of fertility, with injectable contraceptives showing the longest delay. The findings indicated little or no lasting effect of long term use of these methods on fecundability.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of long acting reversible contraceptives has become increasingly common but epidemiologic studies of their effect on return of fertility have been small and inconsistent

Research on use of contraceptives and fertility has focused mainly on the effects of oral contraceptives, with most studies showing short delays in the return of fertility after stopping oral contraceptives

WHAT THIS STUDY ADDS

This study quantified the delay in return of fertility after use of a variety of contraceptive methods

On average, users of injectable contraceptives had the longest delay in return of normal fertility (five to eight menstrual cycles) and users of hormonal and copper intrauterine devices and implant contraceptives had the shortest delays (two menstrual cycles)

Introduction

Worldwide, about 22% of women of reproductive age used hormonal contraception in 2019.[1] In the United States, 35% of women of reproductive age used hormonal contraception in 2015-17.[2] Although male condoms and oral contraceptives remain the most commonly used methods in North America and Europe,[1] long acting reversible contraceptive methods have become increasingly popular.[2] Long acting reversible contraceptive methods include intrauterine devices, implants, and injectable contraceptives.[3] In the US, 2% of women aged 25-34 used long acting reversible contraceptive methods in 1995 compared with 13% of similarly aged women in 2015-17.[2 3] In Europe, 9% of women of reproductive age reported that they used long acting reversible contraceptive methods in 2019.[1]

Most research on the use of contraceptives and fertility has focused on the effect of oral contraceptives on fecundability; the average probability of pregnancy during one menstrual cycle for a couple engaging in regular intercourse without contraception. Several studies reported delays of about three months in return of fertility after stopping oral contraceptives.[4-6] In some[5 7] but not all studies,[4] women who used oral contraceptives for long periods had greater fecundability than women who used oral contraceptives for shorter periods. Less is known about the association between the use of other methods of contraception and fertility, however. Recent use of intrauterine devices (copper and hormonal methods combined) was associated with a slightly longer time to conception than use of barrier methods.[6 8] The results are conflicting,[4 9] however, and could be confounded by parity or underlying fecundity because previous indicators of fertility could affect the choice of contraceptive and the probability of conception in the future. One study indicated that recent use of injectable contraceptives might be associated with delayed conception.[4] Most studies examining less common contraceptive methods

have been small[4 8 9] or retrospective in design, with a risk of recall bias.[6 8] Given the increasing popularity of long acting reversible contraceptive methods and other alternatives to oral contraceptives, more research into their short and long term effects on fertility is needed.

This investigation was designed to examine fecundability in relation to recency and length of use of various hormonal and non-hormonal contraceptive methods, in three large preconception cohorts. The cohorts were from three prospective studies from North America and Denmark of women and men planning pregnancies.

Methods

Study population

We pooled data from three prospective cohort studies of participants planning pregnancies: Snart Gravid, a Danish study of women planning pregnancies, aged 18-49 (2007-11); Snart Foraeldre, an extension of Snart Gravid that included male partners (2011-19); and Pregnancy Study Online (PRESTO), a North American study of women planning pregnancies, aged 21-45, and their male partners (2013-19). Recruitment for Snart Foraeldre and PRESTO is ongoing. Participants in all studies were recruited mainly by advertisements on social media and health related websites, such as Facebook and Netdoktor (www.netdoktor.dk, a well known Danish health related website).[10 11] For example, we used the following advertisement on Facebook to recruit participants for PRESTO: "Trying to conceive? Help scientists learn more about fertility. Enroll in an online research study." The recruitment methods for the study have been described in detail elsewhere.[10-12]

Enrollment and primary data collection were done by email and through the study website. Eligible women were not pregnant, did not use contraceptives, were not receiving fertility treatment, and were trying to conceive. We excluded participants if they reported insufficient or implausible information on their menstrual cycle (Snart Gravid 5%, Snart Foraeldre 8%, PRESTO 2%). We also excluded participants who had been trying to conceive for more than six menstrual cycles at study entry; excluding these participants reduced potential recall bias (that is, differential recall and reporting of exposures and covariates resulting from reduced fertility) and possible confounder misclassification, which might arise if women who had been trying to conceive for longer than six cycles changed their behavior as a result of not conceiving before entering the study. The proportions of women excluded because they had been trying to conceive for more than six cycles were 22% in Snart Gravid, 25% in Snart Foraeldre, and 20% in PRESTO. Participants whose last method of contraception was not included in the present analysis (sterilization that was subsequently reversed, emergency contraception, and douching) were also excluded (<1% of participants). A total of 17 954 participants were included in the pooled analyses: 4435 from the Snart Gravid study, 4768 from the Snart Foraeldre study, and 8751 from PRESTO (fig 1).

All questionnaires were completed online. At baseline, participants reported exposure and covariate information, including personal characteristics, lifestyle factors, and medical history. Follow-up questionnaires were done every two months for 12 months or until a pregnancy was reported, whichever came first. More than 80% of participants completed at least one follow-up questionnaire.All participants provided online informed consent.

Assessment of contraceptive use

At baseline, participants reported the contraceptive method used most recently before they tried to conceive ("Which birth control method did you use most recently?"). Categories included barrier methods (condoms, diaphragm, sponge, foam (Snart Gravid and Snart Foraeldre studies only), jellies, creams, and suppositories), oral contraceptives (progestin only and combined), hormonal intrauterine devices, copper intrauterine devices, patches, injectable contraceptives, vaginal rings, implants, and natural methods (withdrawal, avoiding sex when fertile, calendar methods, and monitoring cervical mucus or basal body temperature). Those who used hormonal methods recently were asked if they waited for a period of time after stopping hormonal contraception before trying to conceive ("Did you wait a few months after stopping hormonal contraception before trying to get pregnant?" If yes, "For how many months did you wait between stopping hormonal contraception and trying to get pregnant?").

To evaluate the potential effects of recent use of hormonal contraceptives, participants who reported waiting longer than one month before trying to conceive after stopping hormonal contraception were categorized as users of barrier or natural methods based on their questionnaire responses. Participants in the Snart Foraeldre and Snart Gravid studies selected only one "most recent" contraceptive method, but participants in PRESTO could select more than one method. Those who reported that they used both hormonal and barrier methods were categorized as users of the hormonal method, and those who reported that they used both barrier and natural methods were categorized as users of barrier methods. Participants who selected more than one hormonal method were categorized based on their reported ages when they stopped.

In PRESTO, participants reported the total number of hormonal contraceptive types they had used in their lifetime (oral contraceptives, rings, implants, injectable contraceptives, patches, hormonal intrauterine devices), the name of each method, and their ages when they started and stopped each method. Length of use (years) was calculated separately for each type of hormonal contraceptive. In the Snart Gravid and Snart Foraeldre studies, a detailed history of length of use was collected only for oral contraceptives.

Assessment of fecundability

We collected data on menstrual cycle dates and pregnancy status from the baseline and follow-up

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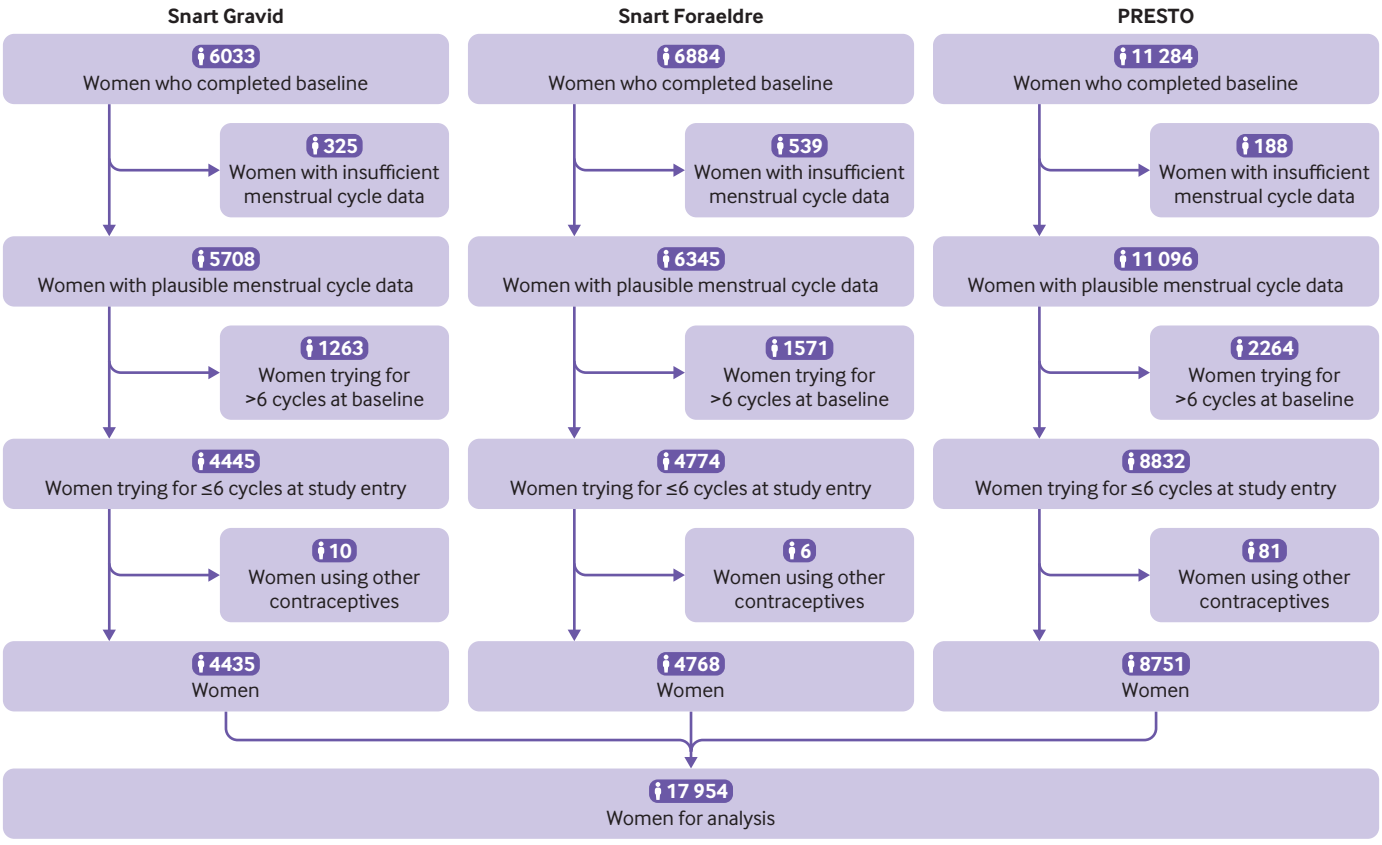

Fig 1 | Flowchart of enrolment and exclusions in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19

questionnaires. At baseline, participants reported the typical length of their menstrual cycle, the date of their last menstrual period, and the number of menstrual periods they had since they began trying to conceive. At each follow-up, women reported the date of their last menstrual period, whether they were pregnant, and whether they had started fertility treatment. In the PRESTO cohort, we also identified pregnancies in participants lost to follow-up by linking to birth registries, searching for baby gift registries and birth announcements online, and contacting the participants directly. We calculated pregnancy attempt time, rounded to the nearest whole cycle, as: (number of menstrual cycles participants had been trying to conceive at baseline)+[(date of last menstrual period from most recent follow-up questionnaire–date of baseline questionnaire)/cycle length]+1.

Assessment of covariates

At baseline, participants reported their age, height, weight, smoking history, education, household income, and frequency of intercourse; length of their relationship; whether they were trying to improve the chances of conception (eg, timing intercourse to their fertile period); length of the menstrual cycle and regularity; parity; history of infertility (previously tried to conceive for ≥12 months); history of physician diagnosed endometriosis, uterine leiomyomata, polycystic ovarian syndrome, or type 2 diabetes; and whether they had ever been pregnant, the outcome of each pregnancy (miscarriage, induced abortion, livebirth), and whether the pregnancy had been planned. We calculated body mass index. In PRESTO, participants also reported their race and ethnicity at baseline. Education and household income were determined differently in the Danish and North American cohorts. To pool the data, we developed similar categories for each cohort by dichotomizing household income at $50 000 (Danish Kr313 845; £38 250; €42 172) per year for the PRESTO cohort and Kr300 000 (£6092; $7963; €6717) per year for the Snart Foraeldre and Snart Gravid studies. Education was reported as years of education after compulsory schooling in the Snart Foraeldre and Snart Gravid studies and as overall years of schooling in PRESTO, and categorized accordingly.

Statistical analysis

Women contributed at risk cycles to the analysis from study entry until they reported a pregnancy, started fertility treatment, withdrew from the study, stopped trying to conceive, were lost to follow-up, or had 12 cycles of trying to conceive, whichever occurred first. We used life table methods to calculate the percentage of couples who conceived during six and 12 cycles of follow-up, accounting for censoring events.[13] We used proportional probability regression models to calculate fecundability ratios with 95% confidence intervals.[14] The fecundability ratio is a measure of the

average probability of conception per cycle comparing users of a specific contraceptive method with a reference group. Proportional probability models adjust for cycle at risk, taking into account the average decline in fecundability as fertile couples conceive and are removed from the population at risk over time.[14] We used the Andersen-Gill data structure to account for left truncation bias that might result from women entering the study after at least one cycle of trying to conceive.[15 16] For example, participants that entered the study after one cycle of trying to conceive, and conceived during the fifth cycle, contributed cycles two to five to the analysis.

We first examined the association between fecundability—the probability of conception per cycle—and use of oral contraceptives (combined and progestin only), hormonal intrauterine devices, copper intrauterine devices, rings, implants, patches, injectable contraceptives, and natural methods as the last method of contraception compared with barrier methods. We selected barrier methods as the reference group because: use of barrier methods would not be expected to cause changes in the vaginal environment or hormone concentrations, offering a well defined contrast with the use of hormonal methods; a large proportion of couples in our study used barrier methods; and we could compare our findings with previous studies that used the same reference category. We then examined fecundability after the use of hormonal intrauterine devices compared with copper intrauterine devices. To quantify delay in return of fertility for each method of contraception, we examined fecundability in each menstrual cycle when participants were trying to conceive. We considered the return of fertility to occur during the cycle in which fecundability for users of a specific method was not meaningfully lower than that for users of barrier methods (that is, adjusted fecundability ratio >0.90). Lastly, we examined the total length of use of each hormonal method. Total length of contraceptive use was divided into two year categories and compared with less than two years of use. In the Snart Foraeldre and Snart Gravid studies, this analysis was conducted only for oral contraceptives because of limited data on length of use.

Models were adjusted for potential confounders measured in the three studies and selected a priori based on the literature and a directed acyclic graph. Potential confounders included cohort (Snart Gravid, Snart Foraeldre, PRESTO); age (<25, 25-29, 30-34, ≥35); education (≤12, 13-15, 16, or ≥17 years in North America or fundamental education, technical education or less than three years of higher education, three to four years of higher education, or greater than four years of higher education in Denmark); non-Hispanic white race and ethnicity (yes *v* no); household income (<*v* ≥$50 000/Kr300 000 annually); current smoker (yes *v* no); body mass index (<25, 25-29, ≥30); baseline intercourse frequency (less than one, one to three, greater than three times a week); trying to improve the chances of conception (yes *v* no); physician diagnosed diabetes (yes *v* no); and lifetime length of use of hormonal contraceptives in months (oral contraceptives only in the Snart Gravid and Snart Foraeldre studies).

We also considered adjustment for possible indicators of underlying fertility because women with a previous pregnancy might be more likely to use a long acting reversible contraceptive method to avoid pregnancy if they believe it is more effective. Also, women with reproductive disorders associated with infertility might make contraceptive choices based on treatment recommendations (eg, use of oral contraceptives to treat polycystic ovarian syndrome[17]). In this analysis, we adjusted for history of unplanned pregnancy (yes *v* no); history of induced abortion (yes *v* no); history of infertility (yes *v* no); menstrual cycle characteristics (irregular cycles, regular cycles of <26 days, regular cycles of 26–30 days, and regular cycles of ≥31 days); parity (parous *v* nulliparous); and physician diagnosed endometriosis (yes *v* no), uterine leiomyomata (yes *v* no), or polycystic ovarian syndrome (yes *v* no). To examine effect measure modification, results for the most recent type of contraception were examined separately by cohort (Denmark *v* North America), age (<30 *v* ≥30), attempt time at study entry (<3 *v* 3-6 menstrual cycles), body mass index (<30 *v* ≥30), history of infertility (yes *v* no), parity (parous *v* nulliparous), and menstrual cycle regularity (regular *v* irregular).

We conducted two sensitivity analyses to evaluate potential bias as a result of misclassification of exposure. We excluded women who stopped hormonal methods of contraception for one or more months before trying to conceive. These women could have switched from hormonal to barrier methods because of concerns that it would take time for the menstrual cycle to normalize after using hormonal contraceptives. Also, we separated progestin only from combined oral contraceptives to consider the potential extent of bias because of analyzing all oral contraceptives in one group. We conducted this analysis in the PRESTO cohort and evaluated the proportion of women who used progestin only oral contraceptives. We also examined the association between recent use of oral contraceptives and fecundability for progestin only and combined oral contraceptives separately.

In each cohort, we used PROC MI to impute missing exposure and covariate values, with over 100 variables in the imputation model to create five datasets. Last method of contraception was imputed for 0.7% of participants in PRESTO and for 0.5% of participants in the Snart Foraeldre and Snart Gravid studies. We also imputed missing outcome data for participants who did not complete any follow-up questionnaires (16% in PRESTO and 13% in Snart Gravid and Snart Foraeldre) to minimize potential selection bias. We assigned these participants one cycle of follow-up and imputed their pregnancy status (pregnant *v* not pregnant) for that cycle. We used PROC MIANALYZE to combine coefficient and standard error estimates across imputed datasets.[18]

Patient and public involvement

No patients were involved in developing the research question, study design, or outcome measures, or in the implementation of this study.

Results

Overall, 17 954 women contributed a total of 10 729 pregnancies during 66 759 menstrual cycles of observation to the analysis. With life table methods, about 56% and 77% of women conceived within six and 12 cycles of follow-up, respectively. After recategorizing participants who reported waiting longer than one month after stopping hormonal contraception, the most commonly reported last method of contraception was oral contraceptives (37.5%), followed by barrier (30.6%) and natural (15.4%) methods (table 1). About 13.3% of women used long acting reversible contraceptive methods, and the most frequently used were intrauterine devices: 7.8% of women used the hormonal intrauterine device and 4.0% of women used the copper intrauterine device as their last method of contraception. The average number of pregnancy attempts before study entry was similar for all contraceptive methods (two menstrual cycles). Users of injectable contraceptives had a higher body mass index on average and were more likely to be current smokers, to report a history of infertility, to have irregular menstrual cycles, and to have type 2 diabetes than users of all other methods of contraception, but were less likely to report trying to improve their chances of conceiving. On average, users of implant, patch, and injectable contraceptives reported fewer years of education and lower household income than users of other methods. Users of intrauterine devices were more likely to be parous and to report a history of unplanned pregnancy than users of other contraceptive methods.

Last method of contraception

Use of injectable contraceptives as the last method of contraception was associated with decreased fecundability compared with use of barrier methods (fecundability ratio 0.65, 95% confidence interval 0.47 to 0.89) after adjusting for personal factors, lifestyle characteristics, and medical history (table 2). This association remained after further adjustment for indicators of underlying fertility (fecundability ratio 0.65, 95% confidence interval 0.47 to 0.89). Users of hormonal intrauterine devices had an increase in fecundability compared with users of barrier methods (fecundability ratio 1.23, 95% confidence interval 1.15 to 1.31) and users of copper intrauterine devices (fecundability ratio 1.19, 95% confidence interval 1.07 to 1.33). These associations were slightly reduced after further adjustment for indicators of underlying fertility. The fully adjusted fecundability ratio was 1.14 (95% confidence interval 1.07 to 1.22) comparing users of hormonal intrauterine devices with users of barrier methods, and 1.18 (95% confidence interval 1.05 to 1.33) comparing users of hormonal intrauterine devices with users of copper intrauterine devices. On average, use of oral contraceptives, copper intrauterine devices, rings, implants, patches, or natural methods as the last method of contraception was not meaningfully associated with fecundability compared with the use of barrier methods as the last method of contraception.

Figure 2 and table 3 show the cycle specific probability of conception and fecundability ratios, respectively, for recent users of different methods of contraception. Compared with users of barrier methods, we found varying delays in return of fertility for recent users of alternative methods. On average, users of injectable contraceptives had the longest delay in return of normal fertility (five to eight cycles), followed by users of patch contraceptives (four cycles), users of oral and ring contraceptives (three cycles), and users of hormonal and copper intrauterine devices and implant contraceptives (two cycles) (table 3). Our results were imprecise for these analyses, however. Because of the small numbers of women who used less common methods, we grouped cycles five to eight and nine to 12 for this analysis.

Overall, associations between last method of contraception and fecundability did not differ widely across cohorts (Denmark *v* North America), age (<30 *v* ≥30), or body mass index (<30 *v* ≥30) (table 4). The results varied by the number of menstrual cycles couples had been trying to conceive at study entry, however: relative to barrier methods, use of oral contraceptives, the patch, and injectable contraceptives was associated with decreased fecundability in women who had been trying to conceive for less than three cycles at study entry, but was associated with improved fecundability in women who had been trying to conceive for three to six cycles. This pattern is consistent with a short term delay in return of fertility. Results were similar across groups when we stratified by history of infertility, parity, and regularity of the menstrual cycle (table 4).

Lifetime duration of use

In the PRESTO cohort, no evidence was found of decreased fecundability with longer total lifetime use of oral contraceptives, rings, injectable contraceptives, hormonal intrauterine devices, implants, or patches (eTable 1). In Snart Gravid and Snart Foraeldre, we found a trend of increasing fecundability with longer lifetime use of oral contraceptives. The adjusted fecundability ratio comparing participants who used oral contraceptives for four to five years with those who used oral contraceptives for less than two years was 1.20 (95% confidence interval 1.05 to 1.36).

Sensitivity analysis

About 18.5% of participants stopped using hormonal methods of contraception and used natural or barrier methods for one or more months before attempting to conceive. The results were consistent when we excluded these women from the main analyses (eTable 2). In PRESTO, about 3.7% of women reported ever having used a progestin only oral contraceptive, and 1.0% of women (n=89) used the progestin only oral contraceptive as their last method of contraception.

Table 1 | Baseline characteristics of participants planning pregnancies by last method of contraception in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19

	Last method of contraception									
Characteristic	Barrier (n=5497, 30.6%)	OC (n=6735, 37.5%)	Hormonal IUD (n=1401, 7.8%)	Copper IUD (n=717, 4.0%)	Ring (n=477, 2.7%)	Implant (n=186, 1.0%)	Patch (n=76, 0.4%)	Injectable (n=94, 0.5%)	Natural* (n=2771, 15.4%)	Total (n=17 954, 100%)
Cohort (%)										
Snart Gravid (n=4435)	20.3	35.2	13.8	13.8	21.4	5.9	19.7	12.6	17.5	24.7
Snart Foraeldre (n=4768)	27.1	31.2	25.6	45.1	19.7	9.6	21.1	3.5	12.6	26.6
PRESTO (n=8575)	52.6	33.6	60.6	41.1	58.9	84.5	59.2	83.9	69.9	48.7
Mean No of pregnancy attempts at study entry (cycles)	2.0	2.1	1.9	1.8	2.1	1.9	2.1	2.3	2.0	2.0
Mean age	29.4	28.6	30.2	30.3	29.1	27.5	27.4	27.7	29.9	29.2
Mean body mass index	26.1	25.5	27.1	25.4	26.4	29.7	26.0	30.6	26.4	26.0
Non-Hispanic white (%)	91.9	95.5	91.5	93.8	91.8	82.8	89.5	75.6	87.4	92.4
Current smoker (%)	9.5	12.8	11.4	14.6	9.1	10.9	15.8	27.0	11.0	11.4
Education less than college degree† (%)	28.5	31.5	30.0	24.8	30.0	44.4	50.6	56.5	30.0	30.2
Household income ($/Kr)‡ (%)										
<50 000/<25 000	17.7	14.4	16.2	15.8	15.7	30.7	22.4	40.7	21.6	17.0
50 000-99 999/25 000-39 999	31.1	27.7	32.8	27.9	32.7	37.3	38.2	31.4	33.8	30.5
100 000-149 999/40 000-64 999	32.6	38.3	29.9	35.1	33.8	24.9	26.3	18.4	28.4	33.9
≥150 000/≥65 000	18.6	19.6	21.1	21.2	17.8	7.1	13.2	9.4	16.3	18.7
Intercourse frequency (times/week) (%)										
<1	21.7	17.0	15.8	15.3	16.7	22.6	27.6	19.3	22.4	19.3
1	19.1	19.0	17.6	20.4	19.9	16.2	13.2	17.1	18.6	18.8
2-3	45.1	45.6	47.1	44.9	47.1	40.6	48.7	31.3	43.2	45.1
≥4	14.1	18.5	19.4	19.4	16.3	20.6	10.5	32.4	15.8	16.8
Mean length of relationship (years)	5.8	5.1	5.4	5.5	4.8	5.1	5.0	4.9	5.7	5.5
Trying to improve chances of conceiving (%)	73.5	62.0	71.0	72.0	64.8	65.1	68.4	57.3	72.6	68.3
History of infertility (%)	8.9	8.4	8.0	7.1	6.1	5.3	15.8	28.0	9.8	8.7
History of unplanned pregnancy (%)	28.5	19.2	31.4	37.1	20.4	27.6	22.4	17.8	31.2	25.8
History of induced abortion (%)	4.9	2.9	5.6	7.1	8.0	9.7	5.3	6.9	7.5	4.9
Menstrual cycle characteristics (%)										
Regular cycles of <26 days	4.6	4.8	4.8	4.2	4.6	2.0	4.0	4.4	4.8	4.7
Regular cycles of 26-30 days	51.4	43.6	38.0	61.0	39.2	25.0	38.2	33.2	54.0	47.5
Regular cycles of >30 days	13.9	11.2	7.3	18.0	5.7	4.1	5.3	3.0	14.7	12.3
Irregular cycles	30.1	40.4	49.9	16.8	50.5	69.0	52.6	59.4	26.5	35.5
Parous (%)	33.7	28.4	50.7	52.1	28.9	46.8	38.2	45.9	35.4	34.1
Endometriosis (%)	1.8	1.7	3.8	1.2	2.3	2.8	2.6	3.9	2.7	2.1
Polycystic ovarian syndrome (%)	6.7	6.1	5.9	6.5	6.6	7.6	13.2	10.6	7.4	6.5
Uterine leiomyomata (%)	1.6	1.3	1.3	1.3	1.7	0.5	5.3	1.0	1.7	1.5
Type 2 diabetes (%)	1.1	0.9	1.9	0.9	0.7	2.7	1.3	5.7	1.0	1.1

OC=oral contraceptives; IUD=intrauterine device.
All characteristics, except for age (across all contraceptive methods) and characteristics of patch users were age standardized at baseline.
*Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.
†Equivalent to fundamental education, technical education, or less than three years of higher education in Denmark.
‡$1.00 (Kr6.28; £0.77; €0.84).

The adjusted fecundability ratio comparing users of a progestin only oral contraceptive with users of barrier methods was 1.09 (95% confidence interval 0.87 to 1.37). Excluding users of progestin only oral contraceptives from the main analyses did not change our results substantially. The adjusted fecundability ratio comparing users of combined oral contraceptives with users of barrier methods was 0.99 (95% confidence interval 0.92 to 1.07).

Discussion

Principal findings

In this large prospective cohort study of couples planning pregnancies and residing in Denmark, Canada, and the US, users of oral contraceptives and some long acting reversible contraceptive methods experienced short term delays in return of fertility compared with users of barrier methods. On average, users of injectable contraceptives had the longest delay in return of normal fertility whereas users of hormonal intrauterine devices, copper intrauterine devices, and implant contraceptives had the shortest delays. Long term use of these methods did not appear to be detrimental to fertility. About 13% of women reported that they used a long acting reversible contraceptive as their last method of contraception, which is consistent with previous descriptions of use of long acting reversible contraceptives in the US.[2 3] Our findings

Table 2 | Last method of contraception and fecundability in participants planning pregnancies in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19

Method	No of cycles	No of pregnancies	Fecundability ratio (95% CI)		
			Model A*	Model B†	Model C‡
Barrier	20 193	3283	Reference	Reference	Reference
Oral contraceptives	25 855	3964	0.93 (0.89 to 0.97)	0.92 (0.88 to 0.96)	0.94 (0.90 to 0.98)
Hormonal IUD	4402	955	1.22 (1.15 to 1.30)	1.23 (1.15 to 1.31)	1.14 (1.07 to 1.22)
Copper IUD	2565	456	1.03 (0.95 to 1.13)	1.03 (0.94 to 1.12)	0.97 (0.89 to 1.06)
Ring	1904	277	0.92 (0.82 to 1.03)	0.91 (0.81 to 1.03)	0.92 (0.82 to 1.03)
Implant	686	109	0.94 (0.78 to 1.13)	1.05 (0.87 to 1.26)	1.03 (0.85 to 1.23)
Patch	286	46	0.94 (0.71 to 1.23)	0.98 (0.75 to 1.29)	1.02 (0.78 to 1.33)
Injectable	416	38	0.59 (0.43 to 0.82)	0.65 (0.47 to 0.89)	0.65 (0.47 to 0.89)
Natural§	10 452	1601	0.96 (0.90 to 1.02)	0.97 (0.92 to 1.04)	0.96 (0.90 to 1.02)
IUDs					
Copper	2565	456	Reference	Reference	Reference
Hormonal	4402	955	1.19 (1.07 to 1.31)	1.19 (1.07 to 1.33)	1.18 (1.05 to 1.33)

IUD=intrauterine device.
*Adjusted only for study (Snart Gravid, Snart Foraeldre, PRESTO).
†Models adjusted for study, age at baseline, education, race, income, body mass index, frequency of intercourse, current smoking, trying to improve chances of conception, diabetes, and length of use of hormonal contraception.
‡Models additionally adjusted for menstrual cycle regularity, length of menstrual cycle, parity, history of unplanned pregnancy, history of induced abortion, history of infertility, endometriosis, uterine leiomyoma, and polycystic ovarian syndrome.
§Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

for use of barrier methods were also consistent with previous studies that reported that 28% of women in the US of reproductive age who are cohabiting, engaged, or married use condoms.[19]

Comparison with other studies and potential mechanisms

The delay in return of fertility that we found was consistent with our previous study examining the use of oral contraceptives in a subset of the present Snart Gravid cohort.[5] Our results were also consistent with several studies that reported slight delays in return of fertility after use of oral contraceptives,[6] intrauterine devices,[6 8] and implants,[4] and longer delays after use of injectable contraceptives.[4 20] We found little association between length of use and fecundability in the PRESTO cohort, but improved fecundability after long term use of oral contraceptives in the Snart Gravid and Snart Foraeldre studies. Our finding in the Snart Gravid and Snart Foraeldre studies is consistent with a retrospective study conducted in 8497 pregnant women in southwest England.[7] This higher fecundability has been attributed to the prevention of ovulation that occurs with use of oral contraceptives,[21] which might help to maintain ovarian reserve.[22 23] Research on this question has shown inconsistent results, however, and potential mechanisms (eg, reduced rates of atresia) have not been fully explained.[24-27]

Recent use of hormonal contraceptives could influence the return of fecundability by several mechanisms. Combined oral contraceptives contain estrogen and progestin, which block the normal release of gonadotropin releasing hormone by the hypothalamus, suppressing production of follicle stimulating hormone and luteinizing hormone, and ultimately suppressing ovulation.[21] Although oral contraceptives have a short half-life, prevention of ovulation, changes in cervical mucus, and thinning of the endometrium could persist after stopping oral contraceptives. The vaginal ring and transdermal patch act by a similar mechanism[28 29] and might continue to suppress ovarian function immediately after stopping use of these contraceptives.[30] Progestin only injectable, implant, and oral contraceptives also act at the pituitary and hypothalamic levels to suppress ovulation and have effects on cervical mucus and endometrial thickness.[21] Also, injectable contraceptives contain substantially higher dosages of progestin than other contraceptive methods as they are designed to prevent pregnancy for at least 90 days after injection.[31 32] The most common type of injectable contraceptive is depot medroxyprogesterone acetate (DMPA), which is given intramuscularly in a 150 mg dose and has a half-life of 50 days. Levels of DMPA are detectable (<100 pg/mL) for 120-200 days after injection.[33] The longer half-life of DMPA could explain the overall reduced fecundability and longer delay in return of fertility in users of injectable contraceptives. Our findings also agree with a previous study that reported a threefold longer time to pregnancy for users of injectable contraceptives than users of condoms after stopping contraception.[4] The characteristics of users of injectable contraceptives differed from those of

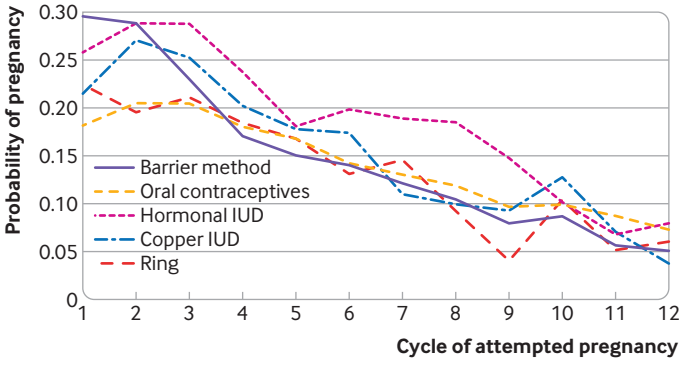

Fig 2 | Per cycle probability of conception for common contraceptive methods in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19. Results are shown for barrier methods and the four most common methods of hormonal contraception. IUD=intrauterine device

Table 3 | Last method of contraception and fecundability in participants planning pregnancies by cycle of attempted pregnancy in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19

Method	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycles 5-8	Cycles 9-12
Barrier						
No of cycles	1229	2317	2356	2294	7833	4164
No of pregnancies	363	671	540	390	1024	295
Adjusted FR (95% CI)*	Reference	Reference	Reference	Reference	Reference	Reference
Adjusted FR (95% CI)†	Reference	Reference	Reference	Reference	Reference	Reference
Oral contraceptives						
No of cycles	1284	2894	3166	3142	10 293	5076
No of pregnancies	234	593	648	568	1459	462
Adjusted FR (95% CI)*	0.66 (0.57 to 0.77)	0.73 (0.66 to 0.81)	0.89 (0.80 to 0.99)	1.06 (0.94 to 1.20)	1.06 (0.98 to 1.14)	1.17 (1.01 to 1.35)
Adjusted FR (95% CI)†	0.69 (0.58 to 0.81)	0.77 (0.70 to 0.85)	0.91 (0.82 to 1.01)	1.07 (0.94 to 1.21)	1.05 (0.97 to 1.14)	1.14 (0.98 to 1.33)
Hormonal IUD						
No of cycles	295	658	643	571	1610	625
No of pregnancies	76	190	185	135	303	66
Adjusted FR (95% CI)*	0.89 (0.72 to 1.10)	0.98 (0.85 to 1.13)	1.25 (1.08 to 1.44)	1.41 (1.18 to 1.68)	1.42 (1.25 to 1.60)	1.47 (1.14 to 1.90)
Adjusted FR (95% CI)†	0.81 (0.65 to 1.00)	0.92 (0.80 to 1.07)	1.20 (1.04 to 1.39)	1.31 (1.09 to 1.57)	1.31 (1.15 to 1.49)	1.40 (1.08 to 1.82)
Copper IUD						
No of cycles	194	355	330	298	931	457
No of pregnancies	42	96	83	60	135	40
Adjusted FR (95% CI)*	0.74 (0.56 to 0.98)	0.97 (0.80 to 1.17)	1.11 (0.91 to 1.36)	1.14 (0.88 to 1.47)	1.08 (0.91 to 1.27)	1.17 (0.85 to 1.61)
Adjusted FR (95% CI)†	0.71 (0.53 to 0.94)	0.93 (0.77 to 1.12)	1.05 (0.85 to 1.29)	1.07 (0.83 to 1.38)	1.02 (0.86 to 1.21)	1.09 (0.78 to 1.51)
Ring						
No of cycles	94	194	228	217	751	420
No of pregnancies	21	38	48	40	103	27
Adjusted FR (95% CI)*	0.82 (0.55 to 1.20)	0.71 (0.52 to 0.95)	0.95 (0.73 to 1.23)	1.05 (0.78 to 1.42)	1.04 (0.86 to 1.27)	0.90 (0.61 to 1.32)
Adjusted FR (95% CI)†	0.78 (0.52 to 1.15)	0.72 (0.54 to 0.97)	0.96 (0.74 to 1.25)	1.05 (0.77 to 1.42)	1.04 (0.86 to 1.27)	0.88 (0.60 to 1.29)
Implant						
No of cycles	40	78	87	84	262	135
No of pregnancies	9	21	15	13	39	12
Adjusted FR (95% CI)*	0.72 (0.41 to 1.30)	0.83 (0.55 to 1.27)	0.73 (0.44 to 1.20)	0.85 (0.48 to 1.49)	1.15 (0.85 to 1.56)	1.34 (0.77 to 2.32)
Adjusted FR (95% CI)†	0.62 (0.34 to 1.11)	0.91 (0.59 to 1.39)	0.86 (0.52 to 1.40)	0.92 (0.53 to 1.62)	1.29 (0.95 to 1.76)	1.34 (0.77 to 2.33)
Patch						
No of cycles	13	32	39	40	112	50
No of pregnancies	1	7	6	7	17	8
Adjusted FR (95% CI)*	0.25 (0.04 to 1.63)	0.67 (0.33 to 1.38)	0.67 (0.32 to 1.41)	0.99 (0.49 to 2.01)	1.19 (0.75 to 1.86)	2.23 (1.17 to 4.25)
Adjusted FR (95% CI)†	0.27 (0.04 to 1.67)	0.71 (0.35 to 1.45)	0.78 (0.37 to 1.62)	1.06 (0.53 to 2.14)	1.28 (0.81 to 2.02)	2.30 (1.20 to 4.42)
Injectable						
No of cycles	14	30	45	50	178	99
No of pregnancies	1	2	1	2	21	11
Adjusted FR (95% CI)*	0.22 (0.03 to 1.45)	0.20 (0.04 to 0.99)	0.13 (0.02 to 0.87)	0.34 (0.10 to 1.20)	0.90 (0.59 to 1.37)	1.72 (0.98 to 3.04)
Adjusted FR (95% CI)†	0.23 (0.04 to 1.44)	0.23 (0.05 to 1.14)	0.13 (0.02 to 0.91)	0.39 (0.11 to 1.36)	0.94 (0.61 to 1.46)	1.81 (1.02 to 3.19)
Natural‡						
No of cycles	553	1199	1271	1245	4006	2178
No of pregnancies	146	289	262	237	519	148
Adjusted FR (95% CI)*	0.89 (0.74 to 1.07)	0.83 (0.73 to 0.95)	0.92 (0.80 to 1.06)	1.13 (0.96 to 1.33)	1.01 (0.91 to 1.12)	1.02 (0.83 to 1.26)
Adjusted FR (95% CI)†	0.90 (0.75 to 1.08)	0.85 (0.75 to 0.97)	0.93 (0.81 to 1.07)	1.07 (0.91 to 1.26)	1.02 (0.92 to 1.14)	0.99 (0.79 to 1.23)

FR=fecundability ratio; IUD=intrauterine device.
*Adjusted for study (Snart Gravid, Snart Foraeldre, PRESTO).
†Models adjusted for study, age at baseline, education, race, income, body mass index, frequency of intercourse, current smoking, trying to improve chances of conception, diabetes, length of use of hormonal contraception, menstrual cycle regularity, length of menstrual cycle, parity, history of unplanned pregnancy, history of induced abortion, history of infertility, endometriosis, uterine leiomyoma, and polycystic ovarian syndrome.
‡Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

users of barrier method in our study, however. Residual confounding by unmeasured factors, such as overall health condition and knowledge of reproductive health, might explain part of the association seen.

The average per cycle probability of conception was about 20% higher in women who used the hormonal intrauterine device than in those who used barrier methods. We expected that women with proven fertility (that is, women with previous pregnancies) would be more likely to use intrauterine devices and to have greater fecundability than women who used barrier methods. Although users of intrauterine devices were more likely to be parous than users of other methods, adjustment for parity and other indicators of underlying fertility did not explain our findings. Also, the fecundability ratio comparing users of hormonal intrauterine devices with users of barrier methods (1.14; 95% confidence interval 1.07 to 1.22) was similar to the fecundability ratio comparing users of hormonal intrauterine devices with users of copper intrauterine devices (1.18; 95% confidence interval 1.05 to 1.33). This finding suggests that users of hormonal intrauterine devices have improved fecundability relative to users of barrier methods and copper intrauterine devices, and that this effect is not confounded by underlying fertility.

Table 4 | Last method of contraception and fecundability in participants planning pregnancies stratified by cohort, age, body mass index, attempt time at study entry, history of infertility, parity, and menstrual cycle regularity in the Snart Gravid, Snart Foraeldre, and PRESTO studies (n=17 954), 2007-19

	Category 1			Category 2		
Method	No of cycles	No of pregnancies	Adjusted FR (95% CI)*	No of cycles	No of pregnancies	Adjusted FR (95% CI)*
Country (Denmark v US and Canada)						
Barrier	8971	1583	Reference	11 076	1675	Reference
Oral contraceptives	17 324	2661	0.90 (0.85 to 0.96)	8333	1275	1.00 (0.93 to 1.07)
Hormonal IUD	1715	368	1.06 (0.96 to 1.17)	2632	560	1.22 (1.11 to 1.33)
Copper IUD	1378	269	0.98 (0.87 to 1.10)	1166	182	0.91 (0.79 to 1.05)
Ring	785	113	0.89 (0.74 to 1.06)	1106	162	0.97 (0.83 to 1.14)
Implant	106	17	0.97 (0.63 to 1.48)	566	85	1.05 (0.85 to 1.29)
Patch	129	19	0.89 (0.59 to 1.35)	155	27	1.11 (0.78 to 1.58)
Injectable	74	9	0.79 (0.43 to 1.45)	345	26	0.63 (0.44 to 0.91)
Natural†	2971	490	0.92 (0.84 to 1.02)	7372	1085	0.98 (0.91 to 1.06)
Age (<30 v ≥30)						
Barrier	13 962	2390	Reference	6231	893	Reference
Oral contraceptives	21 645	3341	0.96 (0.87 to 1.06)	4210	623	1.01 (0.92 to 1.12)
Hormonal IUD	2933	640	1.14 (1.00 to 1.30)	1469	315	1.29 (1.14 to 1.46)
Copper IUD	1840	355	0.94 (0.76 to 1.17)	725	101	0.89 (0.73 to 1.09)
Ring	1370	197	0.91 (0.73 to 1.13)	534	80	1.01 (0.81 to 1.26)
Implant	496	82	1.04 (0.81 to 1.33)	190	27	1.02 (0.70 to 1.48)
Patch	242	37	0.95 (0.61 to 1.50)	44	9	1.42 (0.83 to 2.41)
Injectable	342	32	0.62 (0.41 to 0.93)	74	6	0.59 (0.23 to 1.49)
Natural†	6336	1031	0.99 (0.88 to 1.10)	4116	570	1.00 (0.90 to 1.11)
Body mass index (<30 v ≥30)						
Barrier	15 397	2703	Reference	4796	580	Reference
Oral contraceptives	21 046	3399	0.93 (0.89 to 0.98)	4809	565	0.96 (0.84 to 1.09)
Hormonal IUD	3143	749	1.15 (1.07 to 1.24)	1259	206	1.15 (0.98 to 1.35)
Copper IUD	2129	391	0.98 (0.89 to 1.08)	436	65	0.95 (0.74 to 1.22)
Ring	1470	227	0.92 (0.81 to 1.04)	434	50	0.91 (0.68 to 1.21)
Implant	345	71	1.13 (0.90 to 1.41)	341	38	0.89 (0.65 to 1.21)
Patch	211	35	1.00 (0.74 to 1.36)	75	11	0.95 (0.53 to 1.70)
Injectable	239	30	0.75 (0.53 to 1.06)	177	8	0.44 (0.21 to 0.90)
Natural†	7948	1323	0.96 (0.90 to 1.02)	2504	278	0.96 (0.82 to 1.12)
No of cycle attempts at study entry (0-2 v 3-6)						
Barrier	13 323	2450	Reference	6870	833	Reference
Oral contraceptives	17 307	2804	0.89 (0.85 to 0.94)	8548	1160	1.07 (0.98 to 1.17)
Hormonal IUD	3236	719	1.08 (1.00 to 1.16)	1166	236	1.41 (1.22 to 1.61)
Copper IUD	1833	350	0.96 (0.86 to 1.06)	732	106	1.03 (0.85 to 1.26)
Ring	1261	202	0.91 (0.79 to 1.04)	643	75	0.96 (0.75 to 1.21)
Implant	493	80	0.96 (0.78 to 1.19)	193	29	1.25 (0.87 to 1.78)
Patch	214	33	0.91 (0.67 to 1.25)	72	13	1.43 (0.85 to 2.40)
Injectable	297	30	0.48 (0.32 to 0.74)	119	18	1.15 (0.73 to 1.80)
Natural†	7198	1178	0.92 (0.86 to 0.99)	3254	423	1.08 (0.95 to 1.23)
Infertility (no history v existing history)						
Barrier	18 273	3082	Reference	1920	201	Reference
Oral contraceptives	23 973	3740	0.98 (0.91 to 1.05)	1882	224	1.11 (0.91 to 1.35)
Hormonal IUD	4030	886	1.20 (1.10 to 1.32)	372	69	1.73 (1.32 to 2.26)
Copper IUD	2378	427	0.90 (0.77 to 1.05)	187	29	1.14 (0.78 to 1.67)
Ring	1776	267	0.96 (0.83 to 1.12)	128	10	0.69 (0.32 to 1.52)
Implant	644	105	1.07 (0.86 to 1.33)	42	4	1.20 (0.45 to 3.21)
Patch	249	41	1.03 (0.70 to 1.52)	37	5	1.20 (0.49 to 2.96)
Injectable	306	28	0.58 (0.38 to 0.87)	110	10	1.07 (0.53 to 2.15)
Natural†	9429	1501	0.97 (0.90 to 1.05)	1023	100	1.05 (0.78 to 1.41)
Parity (nulliparous v parous)						
Barrier	14 208	2070	Reference	5985	1213	Reference
Oral contraceptives	19 885	2840	0.95 (0.90 to 1.00)	5970	1124	0.93 (0.86 to 1.00)
Hormonal IUD	2188	443	1.25 (1.13 to 1.37)	2214	512	1.07 (0.97 to 1.17)
Copper IUD	1325	205	0.97 (0.85 to 1.11)	1240	251	0.95 (0.84 to 1.07)
Ring	1423	202	0.98 (0.86 to 1.13)	481	75	0.79 (0.62 to 1.00)
Implant	424	60	0.99 (0.76 to 1.31)	262	49	1.09 (0.85 to 1.40)
Patch	188	27	1.02 (0.71 to 1.45)	98	19	1.04 (0.69 to 1.55)
Injectable	252	24	0.75 (0.51 to 1.11)	164	14	0.53 (0.31 to 0.91)
Natural†	6934	971	0.99 (0.91 to 1.06)	3518	630	0.91 (0.83 to 1.00)

(*Continued*)

Table 4 | Continued

Method	Category 1			Category 2		
	No of cycles	No of pregnancies	Adjusted FR (95% CI)*	No of cycles	No of pregnancies	Adjusted FR (95% CI)*
Menstrual cycle (regular v irregular)						
Barrier	14 221	2356	Reference	5972	927	Reference
Oral contraceptives	15 580	2429	0.95 (0.90 to 1.01)	10 275	1535	0.94 (0.86 to 1.04)
Hormonal IUD	2192	488	1.17 (1.07 to 1.28)	2210	467	1.10 (0.97 to 1.26)
Copper IUD	2205	389	0.96 (0.87 to 1.06)	360	67	1.08 (0.86 to 1.35)
Ring	990	129	0.83 (0.70 to 0.99)	914	148	1.01 (0.87 to 1.16)
Implant	222	35	1.02 (0.75 to 1.40)	464	74	1.03 (0.84 to 1.28)
Patch	127	26	1.19 (0.85 to 1.68)	159	20	0.86 (0.58 to 1.28)
Injectable	236	16	0.51 (0.32 to 0.81)	180	22	0.86 (0.56 to 1.33)
Natural†	7939	1211	0.94 (0.87 to 1.01)	2513	390	1.00 (0.90 to 1.11)

FR=fecundability ratio; IUD=intrauterine device.
*Models were adjusted for study, age at baseline, education, race, income, body mass index, frequency of intercourse, current smoking, trying to improve chances of conception, diabetes, length of use of hormonal contraception, menstrual cycle regularity, length of menstrual cycle, parity, history of unplanned pregnancy, history of induced abortion, history of infertility, endometriosis, uterine leiomyoma, and polycystic ovarian syndrome. Stratified models for age were adjusted for a continuous age variable and stratified models for body mass index were adjusted for a continuous body mass index variable. Models stratified by infertility, parity, and menstrual cycle regularity were not adjusted for the stratification variable.
†Natural methods included withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

Hormonal intrauterine devices release levonorgestrel, a progestin that creates a spermicidal environment and prevents fertilization or implantation. Unlike other hormonal methods, the hormonal intrauterine device does not suppress ovulation.[34] Similarly, the copper intrauterine device prevents fertilization and implantation but has no effect on ovulation. The mechanisms by which copper intrauterine devices prevent pregnancy are not fully understood, however. Most research on intrauterine devices and fecundability has not examined intrauterine devices separately by type,[6 8 9] with the exception of one randomized trial conducted in 1993.[35] In the randomized trial, the investigators evaluated fecundability after removal of the intrauterine device and found slightly higher pregnancy rates in women assigned to the levonorgestrel intrauterine device compared with the copper intrauterine device.

Limitations of the study

This study had several limitations. First, some misclassification of cycles was likely because our calculation of time-to-pregnancy relied on reported length of the menstrual cycle[36] and date of the last menstrual period.[11] Misclassification could also have arisen if participants interpreted the question, "Did you wait a few months after stopping hormonal contraception before trying to get pregnant?" as asking about two or three months specifically. The extent of misclassification is likely to be small, however, because 45% of participants who reported waiting indicated that they waited more than three months, and 16% reported having waited less than 2 months. Second, confidence intervals were wide in the analyses of less commonly used contraceptive methods, limiting our ability to identify the timing of return of fertility. Third, we did not collect data on the date of the last injection for women who used injectable contraceptives. This lack of data limited our ability to determine the recency of use in women who used injectable contraceptives continuously and to evaluate potential misclassification of wait time in women who reported stopping injectable contraceptives a few months before trying to conceive.

In this study, two potential sources of selection bias were identified. Study cohorts were based on self-selection and were volunteers. Women who volunteer to participate in research might differ from those who decline. We believe that our findings are internally valid and externally applicable to those planning pregnancies, however, because the physiological mechanisms underlying the effects that we examined are unlikely to vary substantially between women who did and did not participate. Also, women who conceive immediately after stopping contraception might be less likely to enroll in the study. About 50% of study participants reported that the number of attempts at conceiving was less than two menstrual cycles at study entry, however. This finding indicates that we were successful in recruiting couples at the beginning of their attempts to conceive. We also found minimal evidence of bias in a previous empirical evaluation of the potential for selection bias in Snart Gravid.[37] Overall, we expect any potential selection bias to be minimal.

For our analysis of length of use, two limitations were identified. Precision was limited because a detailed history of use of all types of hormonal contraceptives was available only for participants in PRESTO. Also, reporting of contraceptive methods is likely to be less accurate for methods used in the distant past than those used recently. Given the prospective cohort design, any errors in recall of contraception are expected to be unrelated to outcome, leading to reduced associations for extreme categories of length of contraception use.

Conclusions

In this large prospective investigation, we examined the association between pregravid use of contraceptives and subsequent fecundability. We considered several less studied long acting reversible contraceptive methods, including implants and injectable contraceptives, and also individual intrauterine device types. Our findings suggested that return of normal

fertility varies substantially by contraceptive method. Overall, we found that use of intrauterine devices and implant contraceptives was associated with short delays in the return of fertility, with injectable contraceptives showing the longest delay (about five to eight menstrual cycles). Our results, although imprecise, indicate little or no lasting effect of long term use of these methods on fecundability. As the use of long acting reversible contraceptive methods becomes more common worldwide, these findings might inform clinical recommendations on contraceptive decision making. Understanding the comparative effects of different contraceptives on fecundity is essential for family planning, counselling for contraception, and management of infertility.

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Contributors: JJY was responsible for the statistical analyses, interpretation of the results, manuscript writing, revision, and finalization. KAB was responsible for formulation of the study hypotheses and study design, statistical analyses, interpretation of the results, manuscript writing, and revision. EEH, EMM, and HTS were responsible for study design, development and implementation of the study cohorts, and manuscript revision. AKW was responsible for development and implementation of the study cohorts, statistical analysis, and manuscript revision. KJR and KFH were responsible for study design, analysis methods, interpretation of the results, and manuscript revision. LAW was responsible for study design, development and implementation of the study cohorts, interpretation of the results, manuscript writing, and manuscript revision. JJY was the study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The institutional review board of Boston University Medical Campus approved the study protocol: PRESTO H-31848; Snart Gravid H-25361; Snart Foraeldre H-28795. Because no biological material was included in Snart Gravid and Snart Foraeldre, approval by an ethics committee in Denmark was not required. Snart Gravid was registered by the Danish Data Protection Agency (2013-41-1922) and Snart Foraeldre was registered at Aarhus University to comply with Danish law on data protection (2016-051-000001, No 431).

Data sharing: Data from Snart Gravid, Snart Foraeldre, and PRESTO are not yet publicly available.

The corresponding author attests that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: Results of the study will be accessible to participants and the public through the study websites.

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Web appendix: Supplementary material