Current use of combined hormonal contraception is associated with glucose metabolism disorders in perimenopausal women

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Abstract

Objective

The use of combined hormonal contraceptives (CHCs) worsens glucose tolerance, but the risk for glucose metabolism disorders remains controversial.

Design

The study is a prospective longitudinal population-based cohort study.

Methods

The study was based on a cohort population that comprised 1879 women born in 1966. At age 46, the women answered a questionnaire on contraceptive use and underwent an oral glucose tolerance test. Glucose metabolism indices were evaluated in current CHC (n=153), progestin-only contraceptive (POC, n=842), and non-hormonal contraceptive users (n=884).

Results

In the entire study population, current CHC use was significantly associated with prediabetes (OR 2.0, 95% CI 1.3-3.2) and type 2 diabetes (OR 3.3, 95% CI 1.1-9.7) compared to non-hormonal contraceptive use. After five years of use, the prediabetes risk increased 2.2-fold (95% CI 1.3-3.7) and type 2 diabetes risk increased 4.5-fold (95% CI 1.5-13.5). Compared with the current POC use, current CHC use was significantly associated with prediabetes (OR 1.9, 95% CI 1.2-3.0). Current POC use was not associated with any glucose metabolism disorders. The results prevailed after adjusting for body mass index and socioeconomic status.

Conclusions

CHC use in perimenopausal women was associated with a significantly increased risk of glucose metabolism disorders. This association should be considered in women with increased metabolic risk.

Introduction

Early-generation combined hormonal contraceptives (CHCs) have been shown to negatively impact glucose metabolism, which results in impaired fasting glucose and glucose intolerance (1,2,3). In the past, these preparations contained relatively high doses of ethinyl estradiol (EE; 50-150 μg) and androgenic progestins (4), whereas modern preparations consist of low-dose EE (20-30 μg) and less androgenic or even antiandrogenic progestins (5).

One of our previous studies in young, normal-weight women demonstrated that continuous use of CHCs for nine weeks, regardless of administration route, worsened glucose tolerance and induced chronic inflammation (6). These results are consistent with those of most other studies (7-9) but not all (10). A Cochrane review indicated that CHC use had only a limited effect on glucose metabolism in healthy, normal-weight women (11). However, oral glucose tolerance tests (OGTTs) were not performed in all studies, and only a few of them considered body mass index (BMI). Progestin-only contraceptives (POCs) have been less studied, but they have been associated with minimal (12-16) or no alterations (8,17,18) in glucose metabolism depending on the preparation.

Studies on associations between the risk of type 2 diabetes (T2DM) and CHC use demonstrate conflicting results and are difficult to compare due to differences in study designs, study populations, and hormonal contraceptives (11). However, a moderately elevated risk of diabetes has been observed among premenopausal Chinese women using CHCs (19), and a large prospective population-based Swedish study demonstrated a significantly increased risk of prediabetes (preDM) in current CHC users over 36 years of age (20). The use of CHCs is often long-term, and CHCs are increasingly being prescribed for older women (21,22), as their use has been considered to be safe up to menopause in non-smoking, healthy women with no known risk factors of cardiovascular disease. Thus, currently available data suggest that CHC use increases the risk of diabetes, but whether these risks translate to overt disease remains unclear.

In the present study, we investigated the effects of CHCs, POCs, and non-hormonal contraceptives on the occurrence of preDM and T2DM in perimenopausal women in a prospective, national population-based follow-up cohort.

Subjects and Methods

Study Population

The study population was derived from the unique, prospective, population-based Northern Finland Birth Cohort 1966 (NFBC1966, http://www.oulu.fi/nfbc), which includes all expected births in 1966 in the two northernmost provinces of Finland (n=12 058). Of these, 5889 were female. Enrolment in the database began at the 24th gestational week, and thus far, data has been collected at age 1, 14, 31, and 46 years.

From 2012-2014, a large questionnaire on main health issues and an invitation to a clinical examination was sent to 5123 women of the cohort who were 46 years old. A total of 3708 (72.4%) women responded to the questionnaire, and 3280 of these women (88.5%) also participated in the clinical examination, which included anthropometric measurements and blood samples. After exclusion of participants as described below, all women who answered the questionnaire on current use of hormonal and non-hormonal contraceptives and underwent OGTTs (n=1879) were included in the analyses (Fig. 1). All participants provided informed consent, and the study was approved by the Ethics Committee of the Northern Ostrobothnia District (EETTMK 94/2011).

Current hormonal and non-hormonal contraception (Fig. 1)

Women who attended clinical examinations and reported current use of hormonal or non-hormonal contraceptives were divided into three groups: 1) current CHC (including combined oral contraceptive, vaginal ring, and transdermal patch) users (n=153), 2) current POC (including progestin-only pill,

hormone-releasing intrauterine device, and subdermal capsule) users (n=842), and 3) current users of non-hormonal contraceptives (n=884) as a reference group, which included all women reporting current use of non-hormonal contraceptives (condom, non-hormonal intrauterine device, or their own or their partner's sterilization). Women who reported non-use of any form of contraception (hormonal or non-hormonal) were excluded from the analyses (n=1011), as this group included more multiparous women, who have a higher risk of metabolic disease as a result of multiple pregnancies and deliveries (23,24). Moreover, women using non-identified hormonal preparations (n=8) or hormonal replacement therapy (n=66) and women with formerly diagnosed T2DM (n=68) were excluded from the analysis. The questionnaire also included a question regarding the length of use of the current form of contraception. A total of 143 (94%) CHC users, 796 (98%) POC users, and 512 (58%) non-hormonal contraceptive users reported the length of use. The data were analyzed for less than five years and five or greater years of use.

Anthropometric parameters

All women who participated in the clinical examination were weighed (kg) using a regularly calibrated digital scale. Height (cm) was measured twice using a standard and calibrated stadiometer. Body mass index (BMI) was calculated (kg/m^2) using measured height and weight. Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest.

Laboratory methods

Plasma glucose levels were analyzed with an enzymatic dehydrogenase method, and serum insulin levels were analyzed with a chemiluminometric immunoassay (Advia 1800 and Advia Centaur XP, respectively, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The samples were analyzed in NordLab Oulu, a testing laboratory (T113) accredited by the Finnish Accreditation Service (FINAS) (EN ISO 15189).

Assessment of glucose metabolism disorders

A 2-h 75-g OGTT was performed in all 1879 women after an overnight (12-h) fasting period. The exclusion criteria for the OGTT were medication for diabetes or a measured capillary blood glucose level of >8.0 mmol/l. Both serum insulin and plasma glucose levels were measured at baseline and at 30, 60, and 120 min after glucose intake. Glucose tolerance status was classified according to World Health Organization criteria: 1) normal glucose tolerance (NGT) was defined as having a fasting plasma glucose (FPG) level <6.1 mmol/l and a 2-h glucose level <7.8 mmol/l, 2) impaired glucose tolerance (IGT) was defined as having an FPG level <7.0 mmol/l and a 2-h glucose level of 7.8-11.0 mmol/l, 3) impaired fasting glucose (IFG) was defined as having an FPG level 6.1-6.9 mmol/l and a 2-h glucose level <7.8 mmol/l, and 4) new T2DM was defined as having an FPG level ≥7.0 mmol/l or a 2-h glucose level ≥11.1 mmol/l. Formerly diagnosed cases of T2DM were identified via responses to postal questionnaires (self-reported diagnoses and use of T2DM medication), and the diagnoses were further confirmed from hospital discharge documents and national drug registers of the Social Insurance Institution of Finland. The presence of IFG or IGT was classified as preDM. Women with type 1 diabetes (n=151) or an undefined diabetes type (n=76) were excluded from the analyses.

Fasting glucose and insulin values were used to calculate fasting indexes: homeostasis model assessment of insulin resistance (HOMA-IR) index (fasting plasma glucose (FPG) × fasting serum insulin (FSI) / 22.5) and the homeostasis model assessment of beta-cell function (HOMA2-β) index ((20 × FSI) / (FPG - 3.5) × 100). Glucose and insulin values in OGTTs were used to calculate insulin and glucose areas under the curve (insulin-AUC and glucose-AUC, respectively) and the Matsuda Index for insulin sensitivity (ISI) (10,000 × ((FPG × FSI) × ((FPG + 30 min PG + 60 min PG + 120 min PG) / 4) × ((FSI + 30 min SI + 60 min SI + 120 min SI) / 4)) (Matsuda 1999).

Statistical methods

The differences between study groups were compared with independent Student *t*-tests for normally distributed variables. Variables with a skewed distribution were log-transformed to obtain a normal distribution. The Bonferroni correction was used because there were multiple t-tests. Binary logistic regression modelling was used to investigate whether current use of the different hormonal contraceptives (i.e., CHCs and POCs) was associated with preDM or T2DM by age 46. The factors significantly associated with hormonal contraception use at age 46 were included in multivariate binary logistic regression models. The results of the regression analyses are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). All analyses are reported as crude ORs and ORs adjusted for factors associated with the use of contraceptives and metabolic outcomes (i.e., socioeconomic status (SES), consumption of alcohol, smoking, parity, BMI, and use of cholesterol-lowering medication). IBM SPSS Statistics software (IBM Corporation, 1989, 2013) version 22.0 for Windows was used for all statistical analyses. The level of statistical significance was set at $p \leq 0.05$.

Results

Waist circumferences and BMIs did not differ between CHC, non-hormonal contraceptive, and POC users. CHC users had fewer deliveries than non-hormonal contraceptive users ($p<0.001$) and POC users ($p<0.001$). POC users had fewer deliveries than non-hormonal contraceptive users ($p=0.01$) (Table 1).

Prevalence of glucose metabolism disorders

Current CHC use was significantly associated with preDM (crude OR 2.0, 95% CI 1.3-3.2) and T2DM (crude OR 3.3, 95% CI 1.1-9.7) compared with non-hormonal contraceptive use. The use of CHCs for less than five years was not associated with disordered glucose metabolism compared with the use of non-hormonal contraceptives for less than five years. However, the use of CHCs for five years or more

was associated with an increased risk of preDM when compared with the use of non-hormonal contraceptives for over five years (preDM 20.7% *vs.* 12.3%, crude OR 2.2, 95% CI 1.3-3.7). Furthermore, the use of CHCs for five years or more was associated with an increased risk of T2DM compared with the use of non-hormonal contraceptives (T2DM 4.5% *vs.* 0.7%, crude OR 4.5, 95% CI 1.5-13.5) (Table 2).

A total of 2 (1.3%) CHC users, 16 (2.2%) POC users, and 24 (2.7%) non-hormonal contraceptive users were currently using statins at age 46. As statins may alter glucose metabolism, we performed sub-analyses that excluded statin users, and the risk of preDM or T2DM did not change in any of the groups studied. As for other risk factors for abnormal glucose tolerance, previous gestational diabetes mellitus (GDM) was diagnosed at a similar rate in all study groups: in 9 (5.9%) CHC users, in 71 (8.4%) POC users, and in 69 (7.8%) non-hormonal contraceptive users. Moreover, the family history of T2DM (grandparents, parents, siblings and children) was asked as a part of questionnaire in the clinical examinations. In all study groups, 94-96% answered this question. The family history of T2DM was present in 32% of the CHC users being lower (p=0.001) than in POC (46%) and in non-hormonal contraceptive (48%) users.

In a subgroup analysis, we also investigated a separate group of women who reported CHC use both at age 31 and at age 46 (n=91). The analysis revealed that these women had a two-fold increased risk for preDM (crude OR 2.0, 95% CI 1.0-3.7) but not a significant risk for T2DM compared with non-hormonal contraceptive use at age 46.

In the entire study population, CHC use was significantly associated with preDM (crude OR 1.9, 95% CI 1.2-3.0, adjusted OR 1.8, 95% CI 1.1-3.1) and T2DM (crude OR 2.4, 95% CI 0.8-6.7, adjusted OR 4.1, 95% CI 1.3-13.2) compared with POC use. The use of POCs was not associated with preDM or T2DM when compared with the use of non-hormonal contraceptives (data not shown).

Glucose metabolism according to OGTTs

CHC users had higher glucose AUC values (p=0.01) in OGTT than non-hormonal contraceptive users. CHC users had higher glucose-AUC values (p=0.001) and lower Matsuda Index values (p=0.006) than POC users. The results remained similar after adjustments for BMI and waist circumference (Table 1).

Discussion

This population-based study shows that current use of CHCs at age 46 was associated with an increased risk for glucose metabolism disorders measured by OGTT. The sub-analysis revealed that the use of CHCs for five years or more increased the risk for preDM and T2DM. The current use of POCs was not associated with an increased risk for preDM or T2DM. Although overweight and obesity are known risk factors for glucose metabolism disorders, they did not explain our observations. Also, the previously diagnosed GDM or family history of T2DM did not explain the differences between the study groups.

The present results are consistent with our previous findings in the same cohort population, which showed decreased insulin sensitivity and higher levels of insulin at age 31 in women using CHCs despite lower BMIs in this group (8). The present study shows that some of the current CHC users developed preDM. This observation is in line with the results of a recent Swedish prospective population-based study that included 4794 women aged 36-56 and showed that current CHC use was associated with a four-fold risk of preDM and a seven-fold risk of IGT (20). In addition, a case-control study conducted among Chinese women over 40 years of age demonstrated a 2.1-fold overall risk of T2DM in current premenopausal CHC users, and the risk became significant as early as one year after use (19).

In the present study, a current CHC use duration of five years or more was associated with an increased risk of T2DM compared with non-hormonal contraception use of the same duration, although the clinical value of this finding must be treated with caution due to the low number of diagnosed

T2DM cases. CHC use of less than five years was not associated with any glucose metabolism disorders. The role of the duration of CHC use remains controversial, as some studies have shown no significant correlation between duration and glucose metabolism disorders (25,26), whereas others have suggested a tendency towards an increased risk of diabetes with longer CHC use (19). Variation in study design, hormonal contraceptive preparation, BMI, and ethnicity and inadequate sample sizes in some studies may explain the differences between studies (11). In the present study, the 91 women who reported CHC use at the ages of both 31 and 46 years showed a two-fold increased risk of preDM but not T2DM compared with those who reported non-hormonal contraceptive use at age 46. This finding may be related to the relatively few women using CHCs at both time points, and follow-up of this particular group of women should reveal whether or not these metabolic findings persist and whether the risk of T2DM actually increases compared with that in women using non-hormonal contraceptives or POC. However, the expert panel of the American Diabetes Association (ADA) announced that eventually up to 70% of people with preDM will develop type 2 diabetes (27). In addition, Diabetes Prevention Program (DPP) revealed annualized incidence rate of type 2 diabetes 11% among patients with preDM (28).

Current CHC users exhibited higher glucose-AUCs and lower Matsuda Index values (i.e., they displayed decreased glucose tolerance and insulin sensitivity with compensatory insulin secretion) compared with current POC or non-hormonal contraceptive users. Similarly, earlier studies have shown higher 2-h glucose and fasting insulin levels in CHC users of childbearing age (7,9). Our results fit well with the findings of our previous Finnish randomized, open-label study, which revealed worsened insulin sensitivity during CHC use among healthy, normal-weight women under 33 years of age (6). Similarly, the results of an Italian study showed decreased insulin sensitivity in 30 healthy, lean CHC users (9). The aforementioned and present findings suggest that many CHC users have decreased glucose tolerance, which results in compensatory increased insulin secretion.

CHCs may affect glucose metabolisms by several mechanisms. Reduced glucose tolerance has been linked to hormonal contraceptives containing high-dose EE and androgenic progestins (5). Earlier studies suggest that preparations containing natural estradiol could have a milder effect on glucose tolerance than those containing EE (29-31). Although estrogen is thought to have an independent role, progestin component may also modify the action of estrogen for instance by altering insulin response to glucose (32, 33). In this study the composition of different CHC preparations was not available, and therefore, we could not compare the risk of glucose metabolism alterations between different CHC generations, progestins or difference between EE and estradiol. Previous studies, however, have suggested that newer progestins, such as drospirenone and dienogest, may have less effects on glucose metabolism (29, 34).

In the present study, current POC use was not associated with preDM and/or T2DM compared with non-hormonal contraceptive use. This observation supports the results of earlier studies that showed that POCs have no effect (18) or only mild and clinically non-significant effects on insulin sensitivity (12,13,15). All these studies suggest that POCs have minimal influence on glucose metabolism and may be safer contraceptives than CHCs in regard to T2DM risk. Most studies on the associations between hormonal contraception and alterations of glucose metabolism have mainly involved young, healthy, and non-obese women. Therefore, as overweight status is becoming more common worldwide, more attention should directed toward middle-aged women who start to display unfavorable alterations in body weight, blood pressure, lipid profiles, and glucose metabolism, which together with physical inactivity contribute to an increased risk and incidence of cardiovascular diseases (28,35,36). The present results suggest that POCs should be preferred to CHCs as contraception for women with increased metabolic risk factors.

Strengths and limitations

The greatest strength of this study resides in the characteristics of the study population; the NFBC1966 data set provided a unique opportunity to investigate the association between the use of hormonal contraceptives and glucose metabolism disorders in a large non-selected population of perimenopausal women. In addition, the long-term follow-up of the same population allowed us to compare observations at the ages of 31 and 46. Our results are based on OGTTs, which were performed in all our study participants. We were also able to include several confounding factors in the analysis. There are also limitations, including the fact that data on the current use of hormonal and non-hormonal contraceptives was based on self-reporting. However, the responses were confirmed by another questionnaire during the clinical examinations.

Ninety-four percent of CHC and 98% of PCO users reported the length of use of hormonal preparations whereas only 58% of non-hormonal contraceptive users reported the length of use of non-hormonal contraception. A previous use of CHC among non-hormonal contraception users could have biased our results, as a Swedish study found association between both current and previous use of CHC and prediabetes. The risk was four times higher in current and two times higher in former users hat the beginning of the study when compared to women who had never used CHC. During the 8 years' follow-up, however, previous CHC use did not confer increased risk for abnormal glucose tolerance, and the conclusion was that the possible association between CHC use and abnormal glucose metabolism is transient (20). Likewise, a Chinese study reported that the risk of T2DM decreased after cessation of CHC use in a time-dependent manner (19). Last, the Nurses Health Study found a marginally increased risk of T2DM in previous CHC users (RR 1.10, 95%CI 1.01-1.21), who had stoppes the use at least 5 years earlier, compared with women who had never used CHC (37). Given all this and the fact that in the present study 83% of non-hormonal contraception users had not used any hormonal contraception for the last 5 years minimum, the possibility of CHC affecting glucose tolerance in the non-hormonal contraception users is unlike.

Lastly, women with pre-existing risk factors for impaired glucose metabolism were probably less likely to use CHCs at a perimenopausal age, and therefore, the use of CHCs may be associated with an even greater risk of glucose metabolism disorders in an unselected user population.

The present findings suggest an increased risk for impaired glucose metabolism in current CHC users of perimenopausal age. This finding raises the question whether it is more appropriate to recommend POCs or non-hormonal contraceptives over CHCs to perimenopausal women with known metabolic risks.

Declaration of interest

T.P. has receiver advisory board and lecturing honorarium from Exeltis, Merck, Ferring, and MSD. T.P. also participated in the E4 FREEDOM trial (NCT02817841) with PRA Health Sciences. These affiliations do not conflict with the present research. The remaining authors have nothing to disclose.

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Figure Legends

Figure 1. Flow chart of current use of hormonal and nonhormonal contraceptives

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