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[Intervention Review]

Hormonal versus non-hormonal contraceptives in women with diabetes mellitus type 1 and 2

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ABSTRACT

Background

Adequate contraceptive advice is important in both women with diabetes mellitus type 1 and type 2 to reduce the risk of maternal and infant morbidity and mortality in unplanned pregnancies. A wide variety of contraceptives are available for these women. However, hormonal contraceptives might influence carbohydrate and lipid metabolism and increase micro- and macrovascular complications, so caution in selecting a contraceptive method is required.

Objectives

To investigate whether progestogen-only, combined estrogen and progestogen or non-hormonal contraceptives differ in terms of effectiveness in preventing pregnancy, in their side effects on carbohydrate and lipid metabolism, and in long-term complications such as micro- and macrovascular disease when used in women with diabetes mellitus.

Search methods

The search was performed in CENTRAL, MEDLINE, EMBASE, POPLINE, CINAHL, WorldCat, ECO, ArticleFirst, the Science Citation Index, the British Library Inside, and reference lists of relevant articles. The last search was performed in January 2013. In addition, experts in the field and pharmaceutical companies marketing contraceptives were contacted to identify published, unpublished or ongoing studies.

Selection criteria

Randomised and quasi-randomised controlled trials that studied women with diabetes mellitus comparing: 1. hormonal versus non-hormonal contraceptives; 2. progestogen-only versus estrogen and progestogen contraceptives; 3. contraceptives containing < 50 µg estrogen versus contraceptives containing ≥ 50 µg estrogen; and 4. contraceptives containing first-, second- and third-generation progestogens, drospirenone and cyproterone acetate.

The principal outcomes were contraceptive effectiveness, diabetes control, lipid metabolism and micro- and macrovascular complications.

Data collection and analysis

Two investigators evaluated the titles and abstracts identified from the literature search. Quality assessment was performed independently with discrepancies resolved by discussion or consulting a third review author. Because the trials differed in studied contraceptives, participant characteristics and methodological quality, we could not combine the data in a meta-analysis. The trials were therefore examined on an individual basis and narrative summaries were provided.

Main results

Four randomised controlled trials were included. No unintended pregnancies were reported during the study periods. Only one trial was of good methodological quality. It compared the influence of a levonorgestrel-releasing intrauterine device (IUD) versus a copper IUD on carbohydrate metabolism in women with type 1 diabetes mellitus. No significant difference was found between the two groups. The other three trials were of limited methodological quality. Two compared progestogen-only pills with different estrogen and progestogen combinations, and one also included the levonorgestrel-releasing IUD and copper IUD. The trials reported that blood glucose levels remained stable during treatment with most regimens. Only high-dose combined oral contraceptives and 30 µg ethinylestradiol + 75 µg gestodene were identified as slightly impairing glucose homeostasis. The three studies found conflicting results regarding lipid metabolism. Some combined oral contraceptives appeared to have a minor adverse effect while others appeared to slightly improve lipid metabolism. The copper IUD and progestogen-only oral contraceptives also slightly improved lipid metabolism and no influence was seen while using the levonorgestrel-releasing IUD. Only one study reported on micro- and macrovascular complications. It observed no signs or symptoms of thromboembolic incidents or visual disturbances, however study duration was short. Only minor adverse effects were reported in two studies.

Authors' conclusions

The four included randomised controlled trials in this systematic review provided insufficient evidence to assess whether progestogen-only and combined contraceptives differ from non-hormonal contraceptives in diabetes control, lipid metabolism and complications. Three of the four studies were of limited methodological quality, sponsored by pharmaceutical companies and described surrogate outcomes. Ideally, an adequately reported, high-quality randomised controlled trial analysing both intermediate outcomes (that is glucose and lipid metabolism) and true clinical endpoints (micro- and macrovascular disease) in users of combined, progestogen-only and non-hormonal contraceptives should be conducted. However, due to the low incidence of micro- and macrovascular disease and accordingly the large sample size and long follow-up period needed to observe differences in risk, a randomised controlled trial might not be the ideal design.

PLAIN LANGUAGE SUMMARY

Not enough evidence is available to prove that hormonal contraceptives do not influence glucose and fat metabolism in women with diabetes mellitus

It is important for both women with diabetes mellitus type 1 and type 2 to receive good advice which contraceptive method is best to use. Unplanned pregnancies can lead to serious health issues for both mother and child in women with diabetes. Yet, hormonal contraceptives have been reported to influence glucose and fat metabolism. In this review, both progestogen-only methods (pills and an intrauterine device) and low-dose combined oral contraceptives appeared to have only minor influences on glucose and fat metabolism. However only four studies, most of limited quality, examining a small number of women were included in this review. Only one of the studies reported on true clinical endpoints that is micro- and macrovascular disease. It found no signs or symptoms of thromboembolic incidents or visual disturbances. However this trial was performed over a short period of time. Therefore no definite conclusions can be made based on this review. Future trials analysing glucose and fat metabolism as well as long-term complications for all available contraceptive methods are needed.

BACKGROUND

Pregnancy both in women with diabetes mellitus type 1 and type 2 poses an increased risk of maternal and infant morbidity and mortality. Higher risks of pre-eclampsia, abruptio placentae, polyhydramnios and preterm labour have been described (Girling 2003). In the infant, the risk of congenital malformations, macrosomia, neonatal hypoglycaemia and respiratory distress syndrome is increased (Girling 2003). To reduce these risks, strict diabetic control should be achieved before conception, and adequate contraceptive advice is therefore particularly important to these women (Steel 1997).

The overall use of contraception was found to be similar between women with or without diabetes mellitus (Kimmerle 1994; Kjær 1992). A cohort study identified the use of the following contraceptive methods in women with diabetes mellitus: 30% hormonal contraceptives, 12% intrauterine devices (IUDs), 47% barrier or natural methods or both, and 7% sterilisation (Napoli 2005). No contraception was used in 11% of the diabetic women (Napoli 2005). Very recently a questionnaire survey found women with diabetes mellitus to receive little advice about their contraceptive options (Shawe 2011).

This review considers all types of hormonal contraceptives that are available, combined contraceptives (pills, vaginal ring, contraceptive patch) and progestogen-only methods (pill, implant, injection, IUD), versus the non-hormonal methods (barrier methods, tubal sterilisation, copper IUD). Hormonal contraceptives have been reported to influence carbohydrate and lipid metabolism, whereas non-hormonal contraceptives are unlikely to have any influence.

According to the medical guidelines of the World Health Organization the copper IUD is advised for women with diabetes mellitus with or without further co-morbidity (WHO 2010). These guidelines also state that for the use of low-dose combined oral contraceptives the advantages outweigh the disadvantages for women with diabetes mellitus of up to 20 years' duration and without further co-morbidity. However, in the presence of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease, peripheral vascular disease) complications of diabetes mellitus, progestogen-only contraceptives (pills and IUDs) are preferred to low-dose combined oral contraceptives (WHO 2010).

Adequate contraceptive advice in women with diabetes mellitus is therefore not only important in order to prevent unplanned pregnancies but also to avoid co-morbidity and deterioration of the disease because of the possible side effects of hormonal contraceptives. To date, no review on this topic has included only randomised controlled trials. We have conducted a systematic review to examine the effectiveness and metabolic influences of progestogen-only and combined contraceptives versus non-hormonal methods in women with diabetes mellitus.

OBJECTIVES

Primary objective

To investigate whether there are differences between progestogen-only contraceptive methods, combined estrogen and progestogen contraceptives and non-hormonal contraceptives in terms of

effectiveness in preventing pregnancy, side effects on carbohydrate and lipid metabolism, and long-term outcomes such as micro- and macrovascular complications when used by women with diabetes mellitus.

Secondary objectives

- To investigate whether there are differences between combined oral contraceptive pills and progestogen-only methods in terms of effectiveness in preventing pregnancy, side effects on carbohydrate and lipid metabolism, and long-term outcomes such as micro- and macrovascular complications.
- To investigate whether there are any differences between combined oral contraceptive pills containing < 50 µg estrogen and combined oral contraceptive pills containing ≥ 50 µg estrogen in terms of effectiveness in preventing pregnancy, side effects on carbohydrate and lipid metabolism, and long-term outcomes such as micro- and macrovascular complications.
- To investigate whether there are any differences between oral contraceptives containing first-, second- and third-generation progestogens, drospirenone and cyproterone acetate in terms of effectiveness in preventing pregnancy, side effects on carbohydrate and lipid metabolism, and long-term outcomes such as micro- and macrovascular complications.

METHODS

Criteria for considering studies for this review

Types of studies

All studies using random or quasi-random patient allocation with a minimum treatment period of six months were eligible. The unit of randomisation was either women (individual) or healthcare unit (cluster). Except for the evaluation of effectiveness in preventing pregnancy, crossover studies were eligible for inclusion.

A study is randomised when it appears that the women (or cluster) followed in the study were assigned prospectively to one or two (or more) alternative forms of health care using random allocation. A study is quasi-randomised when it appears that the women (or cluster) were assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth or case record number).

Types of participants

All women of fertile age from all ethnic backgrounds and with diabetes mellitus, types 1 and 2, irrespective of the severity of their illness who desired to use contraception were eligible for inclusion. To be consistent with changes in the classification and diagnostic criteria of diabetes mellitus throughout the years, ideally trials should have established the diagnosis using the standard criteria valid at the time the trial was conducted. The intervention had to be applied to women seeking contraception. Trials enrolling women receiving contraception for non-contraceptive purposes, such as acne vulgaris, were excluded. Studies on women with previous gestational diabetes mellitus and studies on women with impaired glucose intolerance were also excluded from this review.

Types of interventions

Primary interventions

- Any combined oral contraceptive pill, patch or vaginal ring compared with any non-hormonal contraceptive method used in women with diabetes mellitus.
- Any progestogen-only contraceptive (pill, implant, injection, IUD) compared with any non-hormonal contraceptive method used in women with diabetes mellitus.
- Any combined oral contraceptive pill, patch or vaginal ring compared with any progestogen-only contraceptive (pill, implant, injection, IUD) used in women with diabetes mellitus.

Secondary interventions

- Any combined oral contraceptive pill containing $< 50 \mu\text{g}$ estrogen compared with any oral contraceptive pill containing $\geq 50 \mu\text{g}$ estrogen used in women with diabetes mellitus.
- Any oral contraceptive containing first-generation progestogens (generally lynestrenol, norethynodrel, norethisterone) compared with any oral contraceptive containing second-generation progestogens (levonorgestrel, norgestrel) or compared with any oral contraceptive containing third-generation progestogens (desogestrel, gestodene) or compared with any oral contraceptive containing drospirenone or cyproterone acetate used in women with diabetes mellitus.

Types of outcome measures

Main outcome measures

- Contraceptive effectiveness (e.g., cumulative life-table or Kaplan-Meier pregnancy rate, pregnancy Pearl index, proportion of women becoming pregnant)
- Diabetes control and carbohydrate metabolism (e.g., HbA1c, urinary or fasting plasma glucose)
- Lipid metabolism (e.g., cholesterol, triglycerides, low density lipids (LDL), high density lipids (HDL))

Secondary outcome measures

- Continuation rate
- Onset or worsening of microvascular disease (retinopathy, nephropathy, neuropathy)
- Onset or worsening of macrovascular complications (coronary artery disease, cerebral vascular disease, peripheral vascular disease)
- Other serious adverse events

Search methods for identification of studies

See: Additional [Table 1](#) for the search strategy.

Electronic databases were searched using the search strategy outlined below to identify publications that described randomised or quasi-randomised controlled trials comparing contraceptive methods in women with diabetes. The general search strategy for randomised controlled trials (RCTs) and controlled clinical trials (CCTs) was combined with the general search for contraceptive agents as developed by the Cochrane Fertility Regulation Review Group (*The Cochrane Library*) and the general search for diabetes mellitus as developed by the Cochrane Metabolic and Endocrine Disorders Review Group (*The Cochrane Library*). This search strategy was adapted to search the different databases. Databases

that were searched (from their inception to January 2013) included CENTRAL, MEDLINE, EMBASE, POPLINE, CINAHL, WorldCat, ECO and ArticleFirst. The Science Citation Index was searched to identify trials that had cited the studies that were included in the review. The British Library Inside was searched for ongoing trials.

- No language restrictions were used in the searches.
- The reference lists of all identified studies were searched for additional, previously unidentified trials.
- Relevant book chapters and review articles located with the searches or in the reference lists were searched for all relevant trials.
- Authors of all potentially or definitely eligible studies were contacted to find any unidentified published, unpublished or ongoing studies.
- Attempts were made to obtain published, unpublished or ongoing trials from pharmaceutical companies marketing contraceptives.

Data collection and analysis

Assessment of eligibility of the study

The titles and abstracts from the literature search were evaluated by two review authors (JV and MS). If an abstract or full article was available, a study was eligible if it included information on study type (randomised or quasi-randomised controlled trials), diabetes mellitus and contraceptives in women. If only a title was available, the full article was obtained if the title referred to contraceptives and women with diabetes. For all potentially or definitely eligible studies, the full article was obtained and photocopied. Any disagreement about trial selection was resolved by discussion or by consulting the third review author (HV).

Demographics and possible covariates or confounding factors

In addition to the outcomes of interests, the following information was extracted for all eligible studies if noted.

- Study characteristics (e.g., authors; year of publication; inclusion and exclusion criteria; interventions; method of randomisation; allocation concealment; number of participants eligible, randomised and included; blinding; exclusions after randomisation; losses to follow-up; and funding).
- Age: continuous.
- Parity: nulliparous versus multiparous.
- Socioeconomic status ([Erikson 1983](#)).
- Ethnicity.
- Smoking (yes or no).
- Diastolic and systolic blood pressure (mm Hg).
- Length of illness (years).
- Severity of illness: White index ([Heineman 1999](#)).
- Body mass index (BMI) (kg/m^2): continuous,

Assessment of methodological quality

We assessed the validity of all eligible studies using the criteria outlined below.

- Random allocation technique: yes or no.
- Concealment of allocation. Trials were given a quality score (A: adequate, B: unclear, C: inadequate) as described in the

Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2005).

- Blinding of patients and care providers: adequate or not, where appropriate.
- Blinding of outcome assessors: adequate or not, where appropriate.
- Significant differences in loss to follow-up and post-randomisation exclusions.

Two review authors (JV and MS) independently conducted assessment of methodological quality after a pilot test of the assessment. Any disagreement was resolved by discussion or by consulting the third review author.

Data extraction and analysis

Two review authors (JV and MS) extracted data independently. Because the data were not suited to performing a meta-analysis, these two review authors discussed the data in a narrative review. Any disagreement was resolved by discussion or by consulting the third review author.

If, however, in the future more studies are published we will conduct a meta-analysis.

RESULTS

Description of studies

For a detailed description see the table 'Characteristics of included studies'.

Identified trials

The electronic search strategy performed independently by two review authors (JV and MS) identified a total of 796 studies, of which 15 seemed relevant. One further trial was found from handsearching. No response was obtained from letters sent to authors of all potentially or definitely eligible studies or pharmaceutical companies asking for information on published, unpublished or ongoing trials. The whole article was retrieved for these 16 potentially eligible studies.

Excluded studies

Evaluation of the 16 articles by the two review authors led to exclusion of 10 articles of which two described the same trial. Reasons for exclusion were that five publications were case-control studies (Diab 2000; Grigoryan 2008; Petersen 1994; Petersen 1995; Petersen 1996); one article was a review (Skouby 1986b); one article was a case report (Reder 1967); one study was a non-randomised prospective follow-up study (Klein 1999b); one study (Aznar 1976) was performed randomly but included patient with a single impaired glucose intolerance test and no diabetes mellitus was diagnosed during the trial; one study was only randomised for different regimens of using a vaginal ring and did not randomise for different types of contraceptives (Grodnietskaya 2010).

Included studies

Six reports met our inclusion criteria. Two articles were secondary reports of one eligible trial. The remaining four reports were included in the review. Three reports were single-centre studies (Grigoryan 2006; Radberg 1982; Skouby 1986a) and one was a multicentre study (Rogovskaya 2005). The trials took place in

Mexico, Sweden, Russia and USA. The duration of the trials was six or 12 months.

Participants

Three studies included only insulin-dependent diabetic women. Grigoryan 2006 also included women with diabetes mellitus type 2 who were on oral hypoglycaemic therapy. Radberg 1982 and Grigoryan 2006 included women with late diabetic complications, whereas Skouby 1986a and Rogovskaya 2005 excluded these. Grigoryan 2006 included only perimenopausal women.

Interventions

Various contraceptives were examined in the trials reviewed.

Grigoryan 2006 compared IUDs and oral contraceptives composed of:

- 20 µg ethinylloestradiol (EE2) + 150 µg desogestrel (DSG);
- 30 µg EE2 + 150 µg DSG;
- 30 µg EE2 + 75 µg gestodene (GSD);
- T-shaped copper-containing IUD;
- Levonorgestrel (LNG)-releasing IUD.

Radberg 1982 compared oral contraceptives composed of:

- 0.5 mg lynestrenol (LYN);
- 50 µg EE2 + 2.5 mg LYN.

Rogovskaya 2005 compared:

- LNG-releasing IUD;
- copper T 380A IU.

Skouby 1986a compared oral contraceptives composed of:

- 4 mg 17β-estradiol (E2) + 2 mg estriol + 3 mg norethindrone;
- 35 µg EE2 + 500 µg norethindrone;
- 300 µg norethindrone;
- triphasic combination of EE2 + levonorgestrel (LNG) (days 1 to 6: 30 µg EE2 + 50 µg LNG; days 7 to 11: 40 µg EE2 + 75 µg LNG; days 12 to 21: 30 µg EE2 + 125 µg LNG).

There were no trials identified comparing hormonal contraceptives with barrier methods.

Risk of bias in included studies

Grigoryan 2006 compared three different types of oral contraceptives, the T-shaped copper-containing IUD and the LNG-containing IUD. Patients were randomised using a computer-generated scheme. The control group was composed of 40 age-matched women who did not use any methods of contraception. As they were age-matched and not randomised, the results were not included in this review. Allocation concealment was not described. The trial was not blinded. Six women had the T-shaped copper-containing IUD removed after six months due to persistent, frequent intermenstrual bloody discharge. Two women had incomplete expulsion of the T-shaped copper-containing IUD after 5.6 ± 3.7 months. The results for these women were not excluded from the statistical analyses.

Radberg 1982 compared progestogen-only pills with high-dose combined oral contraceptives. The trial had a crossover design. Twenty-five women were randomly assigned to one of the two contraceptives and after six months of treatment and two months of withdrawal they were re-assigned to the other contraceptive. Blinding or allocation concealment was not described. One patient dropped out because of frequent episodes of headache during lynestrenol treatment and one for social reasons. The study was supported by grants from the Swedish Diabetes Association, the Swedish Medical Council and N.V. Organon.

Rogovskaya 2005 compared LNG-releasing IUDs with copper IUDs. Patients were assigned to treatment using random permuted blocks with block sizes of four and six, randomly varied. Computer-generated random numbers were used to select the blocks. Allocation concealment was achieved by having method indicator cards in subsequently numbered, sealed, opaque envelopes that were opened just before intrauterine contraceptive insertion. Patients were not told which contraceptive was inserted. Sixty-two women were enrolled and assigned to a treatment group. One participant did not have the contraceptive inserted and was discontinued from the study. One participant was lost to follow-up and only partial follow-up data were available for five women. The trial was partially supported by Family Health International (FHI) with funds from the U.S. Agency for International Development (USAID). The Moscow office of Schering AG provided the levonorgestrel intrauterine system.

Skouby 1986a compared different types of combined oral contraceptives and progestogen-only pills. Twenty-seven women were randomly divided into four groups. The method of randomisation was not described. After six months of contraceptive use and a washout period of six weeks, eight of the 27 included women were assigned to one or more of the other oral contraceptive regimens. Allocation concealment or blinding was not described. There were no exclusions after randomisation or losses to follow-up registered. The study was supported by The Danish Diabetes Association and a grant from the Ove Villiam Buhl Olesen and Edith Buhl Olesen Memorial Foundation.

Effects of interventions

Four trials were identified comparing 11 different contraceptives. The trials differed in studied contraceptives, participant characteristics and methodological quality so that data could not be combined in a meta-analysis. The trial results were examined on an individual quantitative basis and narrative summaries were provided.

Grigoryan 2006

See Additional [Table 2](#) and [Table 3](#).

This study examined changes in glucose and lipid metabolism. Only perimenopausal women were included. Fifty-eight insulin-dependent women with diabetes mellitus type 1, 10 insulin-dependent women with diabetes mellitus type 2, and 45 women with diabetes mellitus type 2 on oral hypoglycemic therapy were assigned to three different types of combined oral contraceptives, a T-shaped copper-containing IUD, or a LNG-releasing IUD for a period of 12 months.

- Mean insulin requirement increased significantly in women with diabetes mellitus type 1 ($P < 0.001$) using 30 µg EE2 + 75 µg GSD.

One woman with diabetes mellitus type 2 using 30 µg EE2 + 75 µg GSD was switched from oral hypoglycaemic therapy to insulin therapy due to decompensation of her primary disease. During all other interventions the mean insulin requirement and HbA1c remained unchanged.

- Women with diabetes mellitus type 1 and type 2 using 20 µg EE2 + 150 µg DSG showed a statistically significant decrease ($P < 0.05$) of triglycerides and an increase ($P < 0.05$) of HDL cholesterol after 12 months of use. Use of 30 µg EE + 150 µg DSG also resulted in a statistically significant increase ($P < 0.05$) in HDL cholesterol in all women. The blood lipid profile remained unchanged when using 30 µg EE + 75 µg GSD or the LNG-releasing IUD. In women using the T-shaped copper-containing IUD a significant decrease ($P < 0.05$) in total cholesterol level was revealed after 12 months of use.
- Six women had their T-shaped copper-containing IUD removed due to persistent, frequent intermenstrual bloody discharge. Incomplete expulsion of the T-shaped copper-containing IUD occurred in two women and one woman developed pain syndrome. Only one woman with a LNG-releasing IUD complained of menstrual cycle disturbances. This was, however, no reason to remove the IUD. Four women presented with difficulties of a mechanical nature at the time of insertion of the LNG-releasing IUD, and five women appeared to develop pain syndrome. Two women using the LNG-releasing IUD developed acne vulgaris on the back and face, which resolved spontaneously. No cases of inflammatory disease of the small pelvis occurred during the use of any IUD. The side effects of the combined oral contraceptives were minor and were discussed as one group in the article. The observed side effects were: intermenstrual bloody discharge (9.1% to 19.4%); breast enlargement and tenderness (30.3% to 44.4%); gnawing pain in the lower limbs (13.9% to 15.2%); pain in the dextral hypochondrium (5.6% to 12.1%); allergic reaction (0%); and vaginal discharge (45.5% to 75.0%).

Radberg 1982

See Additional [Table 4](#) and [Table 5](#).

This study examined changes in glucose and lipid metabolism. Twenty-three women were assigned to either 0.5 mg LYN or 50 µg EE2 + 2.5 mg LYN, and after six months they were re-assigned to the other preparation.

- Mean insulin requirement remained unchanged during LYN treatment whilst it was significantly increased in the combined oral contraceptive group. In both groups urinary glucose excretion was significantly increased although fasting blood glucose levels did not change. Users of LYN had statistically significant lower mean insulin requirements when compared with EE2 + LYN users after six months ($P < 0.05$).
- Treatment with LYN caused a significant decrease in serum cholesterol, triglycerides, phospholipids and LDL. Combined oral contraceptives on the other hand caused a significant increase in serum triglycerides. Users of LYN had a significantly lower level of serum cholesterol ($P < 0.01$), serum triglycerides ($P < 0.001$), serum phospholipids ($P < 0.001$) and HDL triglycerides ($P < 0.05$) when compared to EE2 + LYN users after six months.
- No signs or symptoms of thromboembolic incidents or visual disturbances were observed during any of the interventions.

- Blood pressure and body weight remained unchanged throughout the study.
- Eleven patients complained of intolerable bleeding irregularities during LYN treatment, and one patient dropped out because of frequent headaches, whilst only two patients complained of bleeding irregularities during the combined oral contraceptive treatment.

Rogovskaya 2005

See Additional Table 6.

This study examined only glucose metabolism. Sixty-two women were randomly assigned to either a copper IUD or a LNG-releasing IUD for a period of 12 months.

- No significant changes in insulin requirement, HbA1c and fasting blood sugars were found during any of the treatments. Also no differences were found in glucose metabolism between the treatment groups after 12 months.
- No adverse effects were reported.

Skouby 1986a

See Additional Table 7.

This study examined changes in glucose and lipid metabolism. Twenty-seven women were assigned to four different oral contraceptive preparations for a period of six months.

- No changes in fasting blood glucose, HbA1c or mean insulin requirements were observed during treatment in any of the groups. Also no differences in glucose metabolism were found between the four different oral contraceptive preparations after six months.
- No changes in triglycerides, LDL cholesterol and very low density lipids (VLDL) cholesterol were observed during treatment in any of the groups. HDL cholesterol was significantly lower after six months in 4 mg E2 + 2 mg estriol + 3 mg norethindrone users. Triglycerides were significantly decreased in 4 mg E2 + 2 mg estriol + 3 mg norethindrone users and the triphasic preparation of EE2 + levonorgestrel users when compared with 35 µg EE2 + 500 µg norethindrone users after six months ($P < 0.01$). VLDL cholesterol was significantly decreased in 4 mg E2 + 2 mg estriol + 3 mg norethindrone users when compared with 35 µg EE2 + 500 µg norethindrone users after six months ($P < 0.01$).
- Blood pressure and body weight remained unchanged throughout the study.
- No adverse effects were reported.

DISCUSSION

Adequate contraceptive advice is important in women with diabetes mellitus in order to prevent unplanned pregnancies carrying an increased risk of maternal and infant morbidity and mortality. This review was performed to identify the most effective type of contraception with the least adverse effects. Four randomised controlled trials were included. Two studies compared hormonal (combined oral contraceptives) and LNG-releasing IUD versus non-hormonal (copper IUD) contraceptives. The two other studies compared combined oral contraceptives with progestogen-only pills. None of the studies compared low-dose combined oral contraceptives with high-dose oral contraceptives.

Effectiveness

No unintended pregnancies occurred during any of the included trials. Since pregnancy is a rare event in contraceptive users, the sample size and duration of the included trials were too small and too short, respectively, to detect differences among the various contraceptives. From large trials conducted among contraceptive users we know that when used perfectly, as in the included trials, combined oral contraceptives and the minipill give a 0.3% chance of experiencing an unintended pregnancy within the first year. This chance is 0.6% for the copper IUD and 0.2% for the progestogen-releasing IUD (WHO 2010). We expect the chance of experiencing an unintended pregnancy is similar for women with diabetes mellitus relative to women without diabetes mellitus.

Diabetes control

Two of the included studies compared diabetes control in women using LNG-releasing IUDs versus copper IUDs (Grigoryan 2006; Rogovskaya 2005). They both found glucose metabolism to remain stable during both interventions. Three of the included studies (Grigoryan 2006; Radberg 1982; Skouby 1986a) compared progestogen-only methods and different types of combined oral contraceptives. They also found no changes in glucose metabolism during use of progestogen-only pills and reported that high-dose oral contraceptives and 30 µg ethinylloestradiol (EE2) + 75 µg desogestrel (GSD) slightly impaired glucose homeostasis. Other low-dose oral contraceptives appeared to have no effect on glucose metabolism.

When interpreting these findings on diabetes control, considerations should be paid to the limitations of the studies. The reporting of the study methods and the methodological quality of the studies was poor. Three of the four included studies did not report the method of generating the allocation sequence, the method of concealing the treatment allocation sequence, and the use of blinding. Non-random methods of generating the allocation sequence, inadequate allocation concealment, not blinding the participants or outcome assessors, and exclusion of participants after randomisation may all result in bias (DerSimonian 1982, Schulz 1995, Schulz 2002a; Schulz 2002b, Schulz 2002c). Furthermore, pharmaceutical companies funded two of the four studies. Studies sponsored by pharmaceutical companies are more likely to have outcomes favouring the sponsor than studies funded by other sources (Lexchin 2003).

In large non-randomised studies, deterioration of glucose tolerance has been described in women using combined oral contraceptives in general (Godsland 1990; Simon 1990; Wynn 1979). This influence does seem minimal with low-dose oral contraceptives and appears to return to normal after the contraceptive is discontinued (Elkind-Hirsch 1994; Wynn 1986). A negative effect on glucose tolerance was not observed in women using progestogen-only pills (Godsland 1992).

Lipid metabolism

The three included studies found conflicting results regarding the outcome lipid metabolism. During one trial, serum cholesterol, triglycerides and phospholipids levels significantly increased in the combined oral contraceptives group while the group of progestogen-only pills showed an opposite effect (Radberg 1982). Although the study authors found a significant change, all lipid levels were within normal range before and after contraceptive use.

The other trial showed no significant changes in lipid metabolism in the treatment groups (Skouby 1986a). Between the users of the different combined oral contraceptive regimens, however, significant differences were found in serum triglycerides and VLDL cholesterol before and after contraceptive use. The third trial (Grigoryan 2006) found a slightly favourable effect on lipid metabolism when using 20 µg EE2 + 150 µg DSG and 30 µg EE + 150 µg DSG with the T-shaped copper-containing IUD after 12 months of use; while use of 30 µg EE + 75 µg GSD and the LNG-releasing IUD resulted in no significant changes. When interpreting these findings, again considerations should be paid to the limitations of the studies as expressed above. Other reports studying lipid metabolism in women with diabetes mellitus have also led to contradictory conclusions. Diab 2000 investigated third-generation low-dose combined oral contraceptives containing gestodene. The trial found low-dose combined oral contraceptives to increase serum triglycerides and very low-density lipoprotein cholesterol levels in women with diabetes mellitus. In contrast, another controlled clinical trial found no evidence of adverse changes in serum levels of lipoproteins in women with well-controlled diabetes mellitus using ethinyl estradiol and gestodene (GSD) (Petersen 1995). Diab 2000 also investigated two progestogen-only methods, Norplant® (implant containing levonorgestrel) and depot medroxyprogesterone acetate (DMPA) administered by injection. From this non-randomised controlled clinical trial they concluded that Norplant resulted in minimal adverse metabolic changes (that is decreased total, low and high-density lipoprotein lipids; unchanged triglycerides). In contrast, DMPA was associated with an unfavourable outcome as fasting blood sugar and total and LDL lipids increased; HDL lipids decreased, and triglycerides remained unchanged. Typically, none of these trials allocated more than 25 women to each intervention, and therefore fell short of statistical power to find a true treatment effect.

True clinical outcomes

Diabetes mellitus is associated with microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease, peripheral vascular disease) complications. Hormones in contraceptives have been reported not only to alter lipoprotein metabolism, insulin levels and tissue insulin resistance (Fontbonne 1989; Godslund 1996) but also blood coagulation, endothelial function and microalbuminuria (Godslund 2000; Monster 2001). All these changes might be related to the development of micro- and macrovascular complications in women with diabetes mellitus (Bass 1993; Fontbonne 1991).

Grigoryan 2006 reported on haemostatic variables. They found that the group of women receiving oral contraception demonstrated a statistically significant decrease in activated partial thromboplastin time and thrombin time after 12 months of use. However this was still within the limits of physiological fluctuations. The use of a copper-containing IUD or LNG-releasing IUD had a neutral effect on the haemocoagulation and fibrinolysis systems. Additionally, one trial (Radberg 1982) included in this review reported on clinical events of true importance, that is micro- and macrovascular disease, the remaining trials investigated the surrogate endpoints like glucose and lipid metabolism. Surrogate outcomes should be considered with caution because they may not always be predictive for the true clinical endpoint (Grimes 2005). Due to the low incidence of micro- and macrovascular complications in contraceptive users, the randomised controlled trial generally does

not suit evaluation of the absolute or relative risk. Radberg 1982 described no signs or symptoms of thromboembolic incidents or visual disturbances during any of the interventions, however the duration of the trial was only six months.

With our search we identified the following observational studies. Klein 1999a performed a cohort study including 484 patients and concluded that the use of oral contraceptives did not affect the severity of diabetic retinopathy or macular edema after 14 years of follow-up. Patients in this study received standard examinations, medical interviews and retinal photography. A multiple logistical regression was performed controlling for other risk factors. However, in this study 33.5% of the patients were lost to follow-up. A retrospective case-control trial studying women using oral contraceptives for one year or longer also concluded there was no increased risk for diabetic retinopathy or nephropathy (Garg 1994). This study however had a small sample size, 43 participants, and there was only one year of follow-up. The main outcome measures were HbA1c, albumin excretion rates and mean retinopathy scores. Another cohort study by Klein 1999b found the use of oral contraceptives to be unrelated to cardiovascular mortality in women with diabetes mellitus after 12 years of follow-up. The study identified 10,135 diabetic patients but selected only 2990 for examination and follow-up. This observational study was initially designed to examine another hypothesis. The power to detect hazard ratios was therefore poor. Although observational, for example case-control and cohort, studies are more prone to bias than randomised controlled trials, and caution should be paid to confounding factors, observational studies might be more appropriate to assess the risk of rare micro- and macrovascular complications (Vandenbroucke 2004).

AUTHORS' CONCLUSIONS

Implications for practice

The four included randomised controlled trials in this systematic review provided insufficient evidence to assess whether progestogen-only and combined contraceptives differ from non-hormonal contraceptives in diabetes control, lipid metabolism and long-term complications. Three of the four studies were of limited methodological quality, sponsored by pharmaceutical companies, and described surrogate outcomes. In the general population second-generation low-dose oral contraceptives appear to be safe (WHO 2009). However, until properly designed trials have been conducted showing no influence of hormonal contraceptives, the copper IUD appears to be the safest choice of contraceptive in patients with diabetes mellitus. The LNG-IUD might be safe to use as well, although no effects on glucose or lipid metabolism were observed.

Implications for research

Ideally, an adequately reported, high-quality randomised controlled trial analysing both intermediate outcomes (that is glucose and lipid metabolism) and true clinical endpoints (that is micro- and macrovascular disease) in users of combined, progestogen-only and non-hormonal contraceptives should be conducted. However, due to the low incidence of micro- and macrovascular disease, and accordingly the large sample size and long follow-up period needed to observe differences in risks, a randomised controlled trial might not be the ideal design.

Observational studies might therefore be more suitable to assess the risks of these rare complications.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Grigoryan 2006

Methods	METHOD OF RANDOMISATION: using a computer-generated scheme ALLOCATION CONCEALMENT: not described BLINDING: not blinded TRIAL DURATION: 12 months
Participants	58 insulin-dependent women with diabetes type 1, 10 insulin-dependent women with diabetes type 2 and 45 women with diabetes type 2 on oral hypoglycaemic therapy. AGE: 39-50 years. LENGTH OF ILLNESS: Diabetes type 1: 10.5-18.1 years. Diabetes type 2: 0.6-10.0 years. INCLUSION CRITERIA: women suffering from diabetes mellitus without evidence of proliferative retinopathy, nephropathy and macrovascular complications. EXCLUSION CRITERIA: women in state of decompensation of the primary disease; ketoacidosis; history of myocardial infarction and/or thromboembolism during the year prior to the study; elevated blood creatinine and urea; nodular form of fibrous-cystic mastopathy; presence of oncological diseases; lack of self-control skills and smoking.
Interventions	1. 20 µg ethinylestradiol and 150 µg desogestrel 2. 30 µg ethinylestradiol and 150 µg desogestrel 3. 30 µg ethinylestradiol and 75 µg gestodene 4. T-shaped copper-containing IUD 5. LNG-releasing IUD
Outcomes	GLUCOSE OUTCOMES: HbA1c; average insulin requirements LIPID OUTCOMES: total cholesterol; triglycerides; LDL cholesterol; HDL cholesterol

Hormonal versus non-hormonal contraceptives in women with diabetes mellitus type 1 and 2 (Review)

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Grigoryan 2006 (Continued)

Notes	No description of sample size or power calculation was provided. The control group was composed of 40 age-matched women who did not use any methods of contraception. As they were age-matched and not randomised, their outcomes were not included in this review. All of the women enrolled completed the study. Women who eliminated the IUD were not excluded from the statistical analyses.
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Radberg 1982

Methods	METHOD OF RANDOMISATION: not described ALLOCATION CONCEALMENT: not described BLINDING: not described TRIAL DURATION: six months. After a washout period of at least six months, the two treatments were crossed over
Participants	25 insulin-dependent diabetic women. AGE: 18-35 years. LENGTH OF ILLNESS: 3-29 years. WHITE CLASSIFICATION: B-F. INCLUSION CRITERIA: - women within 20% of ideal body weight - normotensive - at least two months postpartum. EXCLUSION CRITERIA: - medication known to influence carbohydrate or lipid metabolism within two months before entering the study.
Interventions	1. Lynestrenol 0.5 mg 2. Ethinyl estradiol 50 µg and lynestrenol 2.5 mg
Outcomes	GLUCOSE OUTCOMES: insulin requirement; urinary glucose; fasting blood sugars LIPID OUTCOMES: serum-cholesterol; serum-triglycerides; serum-phospholipids; HDL cholesterol; HDL triglycerides; HDL phospholipids; LDL cholesterol OTHER: body weight, blood pressure
Notes	No description of sample size or power calculation was provided. One patient dropped out because of frequent episodes of headache during lynestrenol treatment and one for social reasons. The study was supported by grants from the Swedish Diabetes Association, the Swedish Medical Council and N.V. Organon.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rogovskaya 2005

Methods	METHOD OF RANDOMISATION: computer-generated random numbers ALLOCATION CONCEALMENT: method indicator cards in sequentially numbered, sealed, opaque envelopes BLINDING: the patients were not told which IUD was inserted TRIAL DURATION: 12 months
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Rogovskaya 2005 (Continued)

Participants	<p>62 insulin-dependent diabetic women. AGE: 18-45 years. PARITY: 1.5-4.5 children. EDUCATION: 11.2-15.6 years. LENGTH OF ILLNESS: 2.2-11.0 years.</p> <p>INCLUSION CRITERIA: - well-controlled insulin-dependent diabetes. EXCLUSION CRITERIA: - retinopathy - nephropathy.</p>
Interventions	<p>1. Levonorgestrel-releasing IUD 2. Copper T 380A IUD</p>
Outcomes	<p>GLUCOSE OUTCOMES: glycosylated hemoglobin levels Fasting serum-glucose levels Daily insulin requirements</p>
Notes	<p>A description of sample size or power calculation was provided. Only glucose metabolism was studied. Outcome data of 59 women was available. One patient did not have the IUD inserted. Two patients were lost to follow up and of five patients only partial data was available. The trial was partially supported by Family Health International (FHI) with funds from the U.S. Agency for International Development (USAID). The Moscow office of Schering AG provided the levonorgestrel intrauterine system.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Skouby 1986a

Methods	<p>METHOD OF RANDOMISATION: not described ALLOCATION CONCEALMENT: not described BLINDING: not described TRIAL DURATION: six months</p>
Participants	<p>27 insulin-dependent diabetic women. AGE: 17-35 years. INCLUSION CRITERIA: - weight within 20% of ideal - blood pressure <140/90 mm Hg. EXCLUSION CRITERIA: - late diabetic complications - use of hormonal contraceptives within 6 weeks of entering the trial.</p>
Interventions	<p>1. 4 mg 17β-estradiol, 2 mg estriol and 3 mg norethindrone 2. 35 μg ethinyl estradiol + 500 μg norethindrone 3. 300 μg norethindrone 4. triphasic combination of ethinylestradiol (30, 40, 30 μg) + levonorgestrel (50, 75, 125 μg) for 6/5/10 days</p>

Skouby 1986a (Continued)

Outcomes	GLUCOSE OUTCOMES: fasting plasma glucose; 24-hour-insulin requirement; HbA1c levels. LIPID OUTCOMES: plasma free fatty acids; triglycerides; total cholesterol; HDL; LDL; VLDL. OTHER: body weight; blood pressure
Notes	No description of sample size or power calculation was provided. No loss to follow up was reported. 8 of the 27 women were shifted to one or more of the other oral contraceptive regimens after a washout period of six weeks. The study was supported by The Danish Diabetes Association and a grant from Ove Villiam Buhl Olesen and Edith Buhl Olesen Memorial Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aznar 1976	participants had only an impaired glucose tolerance test but no diabetes mellitus
Diab 2000	case-control study
Grigoryan 2008	case-control study
Grodnitskaya 2010	it was only randomised for different regimens of using a vaginal ring and did not randomise for different types of contraceptives
Klein 1999b	non-randomised study
Petersen 1994	case-control study
Petersen 1995	case-control study
Petersen 1996	case-control study
Reder 1967	case report
Skouby 1986b	review

ADDITIONAL TABLES
Table 1. Search strategy

#1 Diabetes search ((((((((((((("diabetes mellitus"[MESH] OR "diabet*"[title/abstract word]) OR (DKA[title/abstract word] OR

Table 1. Search strategy (Continued)

```

IDDM[title/abstract word] OR
DM1[title/abstract word])) OR
(MODY[title/abstract word]OR
DM2[title/abstract word] OR
NIDDM[title/abstract word] OR
IIDM[title/abstract word])) OR
"insulin* secret* dysfunc*"[title/abstract word]) OR
"insulin* resist*"[title/abstract word]) OR
(("impaired glucose tolerance"[title/abstract word] OR
"glucose intoleran*"[title/abstract word] OR
"insulin* resist*"[title/abstract word]) AND
(DM[title/abstract word] OR
DM2[title/abstract word])))) OR
("insulin* depend*"[title/abstract word] OR
"insulindepend*"[title/abstract word] OR
"insulin-depend*"[title/abstract word])) OR
("non insulin* depend*"[title/abstract word] OR
"noninsulindepend*"[title/abstract word] OR
"noninsulin-depend*"[title/abstract word] OR
"non insulin-depend*"[title/abstract word] OR
"noninsulin depend*"[title/abstract word] OR
"non-insulindepend*"[title/abstract word])) OR
(("typ* 1"[title/abstract word] OR
"typ* I"[title/abstract word]) AND
DM[title/abstract word])) OR
(("typ* 2"[title/abstract word] OR
"typ* II"[title/abstract word]) AND
DM[title/abstract word])) OR
((juvenil*[title/abstract word] OR
child*[title/abstract word] OR
keto*[title/abstract word] OR
labil*[title/abstract word] OR
brittl*[title/abstract word] OR
"early onset"[title/abstract word]) AND
(DM[title/abstract word] OR
DM1[title/abstract word])))) OR
(("keto* prone"[title/abstract word] OR
"autoimmun*"[title/abstract word] OR
"sudden onset"[title/abstract word]) AND
(DM[title/abstract word] OR
DM1[title/abstract word])))) OR
(("keto* resist*"[title/abstract word] OR
"nonketo"[title/abstract word] OR
"non keto"[title/abstract word] OR
"adult* onset"[title/abstract word] OR
"matur* onset"[title/abstract word] OR
"late* onset"[title/abstract word] OR
"slow onset"[title/abstract word] OR
"stabl*"[title/abstract word]) AND
(DM[title/abstract word] OR
DM2[title/abstract word])))) OR
"Insulin Resistance"[MESH]) OR
("insulin* defic*"[title/abstract word] AND
(absolut*[title/abstract word] OR
relativ*[title/abstract word])))) OR
"metabolic* syndrom*"[title/abstract word]) NOT
("Dermatomyositis"[MESH] OR
"Myotonic Dystrophy"[MESH] OR
("Diabetes Insipidus"[MESH] NOT
("Diabetes Mellitus"[MESH] OR
mellitus[title/abstract word]))))

```

Table 1. Search strategy (Continued)

#2 Contraceptives search

```

((((((((("Contraceptive Agents, Female"[MESH] OR
(contraceptive[title/abstract word] AND
device*[title/abstract word])) OR
(oral[title/abstract word] AND
contraceptive*[title/abstract word])) OR
(progestagen[title/abstract word] OR
progestogen[title/abstract word] OR
progesteron*[title/abstract word] OR
levonorgestrel[title/abstract word] OR
norethisteron*[title/abstract word] OR
norethindron*[title/abstract word] OR
norgestimat*[title/abstract word] OR
desogestr*[title/abstract word] OR
gestode*[title/abstract word] OR
norgestrel[title/abstract word])) OR
(estrogen*[title/abstract word] OR
estrage[n]*[title/abstract word] OR
oestrogen*[title/abstract word] OR
oestrage[n]*[title/abstract word])) OR
(ethinyl[title/abstract word] AND
(estradiol[title/abstract word] OR
oestradiol[title/abstract word])))) OR
((estrogen*[title/abstract word] OR
estrage[n]*[title/abstract word] OR
oestrogen*[title/abstract word] OR
oestrage[n]*[title/abstract word] OR
(ethinyl[title/abstract word] AND
(estradiol[title/abstract word] OR
oestradiol[title/abstract word])))) AND
(low[title/abstract word] AND
dose[title/abstract word])))) OR
(progestagen-only[title/abstract word] OR
progestogen-only[title/abstract word] OR
progesteron-only[title/abstract word] OR
norplant[title/abstract word])) OR
"barrier method"[title/abstract word]) OR
(IUD*[title/abstract word] OR
IUS*[title/abstract word] OR
(intra-uterine[title/abstract word] AND
(system[title/abstract word] OR
systems[title/abstract word] OR
device*[title/abstract word])))) NOT
("Menopause"[MESH] OR
"Estrogen Replacement Therapy"[MESH] OR
"Neoplasms"[MESH])

```

#3 RCTs search

```

((((((((((((((((((((("randomized controlled trials"[MESH:noexp] OR
"random allocation"[MESH:noexp]) OR
"double-blind method"[MESH:noexp]) OR
"single-blind method"[MESH:noexp]) OR
"clinical trials"[MESH]) OR
"placebos"[MESH:noexp]) OR
"research design"[MESH:noexp]) OR
"comparative study"[MESH]) OR
"evaluation studies"[MESH]) OR
"follow-up studies"[MESH]) OR

```

Table 1. Search strategy (Continued)

```
"prospective studies"[MESH]) OR
"cross-over studies"[MESH]) OR
"intervention studies"[MESH]) OR
"randomized controlled trial"[pt]) OR
"controlled clinical trial"[pt]) OR
"clinical trial"[pt]) OR
"clinic* trial*"[title/abstract word]) OR
((((("singl*"[title/abstract word] OR
"doubl*"[title/abstract word]) OR
"tripl*"[title/abstract word]) OR
"trebl*"[title/abstract word]) AND
("blind*"[title/abstract word] OR
"mask*"[title/abstract word])))) OR
"placebo*"[title/abstract word]) OR
"random*"[title/abstract word]) OR
"latin square"[title/abstract word]) OR
"control*"[title/abstract word]) OR
"prospectiv*"[title/abstract word]) OR
"volunteer*"[title/abstract word]) NOT
("animal"[MESH] NOT
"human"[MESH]))
```

#4 Diabetes Mellitus with Hormonal Contraceptives and RCTs
Search #1 AND #2 AND #3

#5 Adverse events
"probability" [MESH] OR
(risk*[WORD] OR
cohort*[WORD] OR
follow-up[WORD] OR
predict*[WORD] OR
case-control*[WORD]) OR
(cause*[WORD] OR
causat*[WORD] OR
causing[WORD] OR
causal*[WORD] OR
etiol*[WORD] OR
aetiol*[WORD]) OR
"case-control studies"[MESH]

#6 Diabetes Mellitus with Hormonal Contraceptives and Adverse events
Search #1 AND #2 AND #5

Table 2. Results Grigoryan 2006 diabetes mellitus type 1

	Hba1c	Total cholest- terol	Total triglyc- erides	HDL-Cholesterol	LDL-cholesterol
Before 20 µg EE2 + 150 µg DSG	7.5±0.3	6.88±0.95	0.88±0.75	1.68±0.68	2.75±0.85
After 20 µg EE2 + 150 µg DSG	7.5±0.4	7.02±1.25	0.81±0.55 (P<0.05)	1.89±1.12 (P<0.05)	2.84±1.13
Before 30 µg EE2 + 150 µg DSG	7.5±0.3	7.78±1.45	0.86±0.37	1.66±0.68	2.75±0.75
After 30 µg EE2 + 150 µg DSG	7.5±0.6	7.72±1.23	0.88±0.57	1.75±0.50	2.83±0.76

Hormonal versus non-hormonal contraceptives in women with diabetes mellitus type 1 and 2 (Review)

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Table 2. Results Grigoryan 2006 diabetes mellitus type 1 (Continued)

(P<0.05)

Before 30 µg EE2 + 75 µg GSD	7.5±0.3	7.87±1.75	0.76±0.37	1.68±0.68	2.95±0.55
After 30 µg EE2 + 75 µg GSD	7.5±0.4	7.65±0.29	0.78±1.57	1.70±1.63	2.89±0.66
Before copper IUD	7.8±0.3	not available	not available	not available	not available
After copper IUD	7.8±0.7	not available	not available	not available	not available
Before LNG-IUD	7.6±0.5	not available	not available	not available	not available
After LNG-IUD	7.7±0.3	not available	not available	not available	not available

Table 3. Results Grigoryan 2006 diabetes mellitus type 2

	Hba1c	Total cholesterol	Total triglycerides	HDL-Cholesterol	LDL-cholesterol
Before 20 µg EE2 + 150 µg DSG	7.7±0.4	7.14±0.93	0.91±1.14	1.58±0.82	2.76±0.63
After 20 µg EE2 + 150 µg DSG	7.6±0.3	7.28±1.14	0.88±0.51	1.62±0.91	2.72±0.45
			(P<0.05)	(P<0.05)	
Before 30 µg EE2 + 150 µg DSG	7.6±0.5	7.84±1.32	0.87±0.54	1.51±0.83	2.86±0.63
After 30 µg EE2 + 150 µg DSG	7.5±0.7	7.64±0.84	0.87±1.21	1.68±0.64	2.80±1.45
				(P<0.05)	
Before 30 µg EE2 + 75 µg GSD	7.3±0.4	7.74±1.82	0.72±1.53	1.56±0.83	3.13±0.63
After 30 µg EE2 + 75 µg GSD	7.4±0.7	7.64±1.84	0.72±1.81	1.57±1.92	2.93±1.45
Before copper IUD	7.5±0.7	not available	not available	not available	not available
After copper IUD	7.4±0.3	not available	not available	not available	not available
Before LNG-IUD	7.4±0.6	not available	not available	not available	not available
After LNG-IUD	7.6±0.6	not available	not available	not available	not available

Table 4. Results Radberg 1982, glucose outcomes

	daily insulin dosage	urinary glucose	blood glucose
Before 0.5 mg LYN	43.9±3.1	180±30	10.5±0.9
After 0.5 mg LYN	43.1±3.0	270±45 (p<0.05)	10.5±0.9
Before 50 µg EE2 + 2.5 mg LYN	42.1±3.2	237±45	10.1±0.6

Table 4. Results Radberg 1982, glucose outcomes *(Continued)*

After 50 µg EE2 + 2.5 mg LYN	44.9±3.4 (p<0.01)	302±47 (p<0.05)	10.6±0.7
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Table 5. Results Radberg 1982, lipid outcomes

	serum choleste- rol	serum triglyce-rides	serum phos- pho-lipids	HDL choleste-rol	HDL triglyce- rides	HDL phos- pho-lipids	LDL choleste-rol
Before 0.5 mg LYN	5.17±0.16	0.66±0.1	2.77±0.09	1.28±0.06	0.09±0.02	1.07±0.05	3.33±0.13
After 0.5 mg LYN	4.56±0.12 (p<0.001)	0.46±0.05 (p<0.001)	2.45±0.07 (p<0.01)	1.23±0.04	0.06±0.01	1.05±0.03	3.10±0.1 (p<0.01)
Before 50 µg EE2 + 2.5 mg LYN	4.89±0.22	0.63±0.1	2.71±0.09	1.20±0.04	0.07±0.01	1.13±0.08	3.42±0.18
After 50 µg EE2+ 2.5 mg LYN	4.91±0.23	0.75±0.11 (p<0.05)	2.84±0.06	1.22±0.05	0.08±0.02	1.21±0.08	3.22±0.22

Table 6. Results Rogovskaya 2005

	HbA1c	fasting glucose	daily insulin dosage
Before LNG- IUD	5.6±1.3	5.2±0.9	35.2±12.7
After LNG- IUD	6.3±1.5	7.4±4.2	35.1±12.8
Before Copper- IUD	5.5±1.4	5.0±0.6	36.4±9.7
After Copper- IUD	6.3±1.3	7.5±4.2	36.4±9.0

Table 7. Results Skouby 1986

	fasting glu- cose	HbA1c	daily insulin dosage	free fatty acids	serum triglyc- erides	HDL choles- terol	LDL choles- terol	VLDL cho- lesterol
Before 4 mg E2 + 2 mg estriol + 3 mg norethin- drone	15.6±1.9	8.6±0.7	51±6	986±151	1.07±0.2	1.54±0.1	3.17±0.4	0.49±0.1
After 4 mg E2 + 2 mg estriol + 3 mg norethindrone	14.6±2.0	8.8±0.4	55±5	1033±145	0.95±0.1	1.33±0.1 (p<0.01)	3.12±0.4	0.41±0.1
Before 35 µg EE2 + 500 µg norethindrone	12.8±1.8	9.5±0.7	48±4	854±99	1.28±0.2	1.42±0.1	3.13±0.3	0.58±0.1
After 35 µg EE2 + 500 µg norethindrone	12.9±2.2	9.1±0.7	50±4	756±118	1.93±0.3	1.52±0.1	3.48±0.4	0.88±0.1
Before 300 µg norethindrone	14.1±1.7	8.9±0.5	47±3	969±138	1.25±0.1	1.23±0.1	3.26±0.2	0.57±0.1
After 300 µg norethindrone	16.9±2.0	9.5±0.9	47±3	783±123	1.17±0.1	1.30±0.1	3.15±0.2	0.53±0.1
Before triphasic preperation of EE2 + lev- onorgestrel	17.1±1.7	9.1±0.5	45±5	594±61	1.25±0.3	1.51±0.1	3.23±0.2	0.57±0.1
After triphasic preperation of EE2 + lev- onorgestrel	13.2±1.5	9.1±0.5	44±4	761±105	1.12±0.2	1.54±0.1	3.35±0.3	0.53±0.1

WHAT'S NEW

Date	Event	Description
22 January 2013	New citation required but conclusions have not changed	No new randomised controlled trials included. Conclusions not changed.
18 December 2008	New search has been performed	Included one randomised controlled trial. Conclusions not changed.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 4, 2006

Date	Event	Description
15 April 2008	Amended	Converted to new review format.
6 June 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

J Visser: lead reviewer, protocol development, searching for trials, quality assessment of trials, data extraction, data analysis and drafted the review

M Snel: protocol development, searching for trials, quality assessment of trials, data extraction, data analysis and drafted the review

HAAM van Vliet: protocol development, input at all other stages of review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No source of support provided, Not specified.

External sources

- No source of support provided, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Glucose [metabolism]; Contraceptive Agents, Female [*administration & dosage] [adverse effects]; Contraceptives, Oral, Hormonal [*administration & dosage] [adverse effects]; Diabetes Mellitus, Type 1 [*blood]; Diabetes Mellitus, Type 2 [*blood]; Homeostasis [drug effects]; Intrauterine Devices, Medicated; Levonorgestrel [administration & dosage] [adverse effects]; Lipid Metabolism [drug effects]; Progestins [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy