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Long versus short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS (Review)

Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P

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[Intervention Review]

Long versus short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS

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ABSTRACT

Background

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women. Apart from infertility, women with PCOS often have other endocrine disorders, including insulin resistance, hyperinsulinaemia and hyperandrogenism. Metformin,combined with clomiphene citrate (CC), has been shown to be more effective in ovulation induction when compared with clomiphene citrate alone. The optimal duration for metformin pretreatment before initiation of clomiphene citrate, however, is unknown.

Objectives

To determine the effectiveness of short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile women with PCOS.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, EMBASE and PsycINFO (all from inception to 1 February 2012).

Selection criteria

Randomised controlled trials comparing short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC for ovulation or achievement of pregnancy in infertile women with PCOS.

Data collection and analysis

No trials were found that met the selection criteria.

Main results

No randomised controlled trials were identified.

Authors' conclusions

There are insufficient data to determine whether short-course metformin pretreatment is as effective as the conventional long-course metformin pretreatment before initiation of clomiphene citrate for ovulation induction in infertile women with PCOS. A well-designed randomised controlled trial is needed to answer this important clinical question.

PLAIN LANGUAGE SUMMARY

Long versus short course treatment with Metformin + Clomiphene Citrate for ovulation induction in women with PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive-age. Apart from infertility, women with PCOS often have other endocrine disorders, including insulin resistance, hyperinsulinaemia and hyperandrogenism. Metformin combined with clomiphene citrate (CC), has been shown to be more effective in ovulation induction than clomiphene citrate alone. The optimal duration for metformin pretreatment before initiation of clomiphene citrate, however, is unknown. There have been no trials conducted to determine the effectiveness of short-course (less than four weeks) metformin plus clomiphene citrate compared to the conventional long-course (four weeks or more) metformin plus clomiphene citrate with regard to ovulation and achievement of pregnancy in infertile women with polycystic ovary syndrome.

BACKGROUND

Description of the condition

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women and affects approximately 5 to 10% of this population group (Hull 1987; Polson 1988). It is also the most common cause of anovulatory infertility.

Description of the intervention

Clomiphene citrate (CC) is currently the first-line, most widely used, oral medication to induce ovulation in women with PCOS (Kim 2000). However, only 70 to 85% of women with PCOS respond to clomiphene citrate, with a pregnancy rate of only 30 to 40% (Lobo 1982; Franks 1995). This could be attributed to the anti-estrogenic effect of clomiphene citrate on cervical mucous and endometrium (Randall 1991; Nakamura 1997).

How the intervention might work

PCOS is also associated with metabolic abnormalities, in part mediated through peripheral insulin resistance and subsequent hyperinsulinaemia. Metabolic abnormalities are more common in obese compared with lean women with PCOS. Different techniques of measuring insulin resistance provide varying estimates of insulin resistance in PCOS. Up to 50-100% of obese and 22% of lean women with PCOS may have insulin resistance (Dale 1992). Hyperinsulinaemia to lead to hyperandrogenism, which may adversely affect follicular development and ovulation (Barbieri 1986; Nestler 1998a). Metformin is a medication that has an insulin-sensitizing effect and is widely used in non-insulin dependent diabetes mellitus. Metformin could also ameliorate hyperandrogenism in women with PCOS (Nestler 1998b; Pirwany 1999) and thus possibly correct the endocrinopathy. Several studies have demonstrated that treatment with metformin before administration of clomiphene citrate in women with PCOS may significantly increase ovulation and pregnancy rates (Velazquez 1994; Vandermolen 2001). The most recent research synthesis revealed that metformin was 50% better than placebo for increasing ovulation in infertile women with PCOS and that metformin plus clomiphene citrate may be three to four-fold superior to clomiphene citrate alone for producing ovulation and achievement of pregnancy (Kashyap 2004). The same study, however, showed that metformin alone had no confirmed benefit over placebo for achievement of pregnancy.

Why it is important to do this review

Although it has become clear that the combination of metformin and clomiphene citrate is more effective in achieving pregnancy than clomiphene citrate (CC) alone (Kashyap 2004; Lord 2004), the optimal duration of metformin pretreatment before CC administration in women with PCOS is unknown. Previous stud-

ies usually used four to 12 weeks of metformin before beginning clomiphene citrate (Velazquez 1994; Vandermolen 2001), but many women found such duration of metformin pretreatment inconvenient. Long-term use of metformin may also be associated with adverse effects such as lactic acidosis and gastrointestinal disturbances (Lord 2004). One study recently revealed that ultra-short (12 days) metformin pretreatment before administration of CC significantly increased ovulation and pregnancy rates compared to CC alone (Hwu 2005). It is of interest, therefore, to determine whether short-course (less than four weeks) metformin treatment in conjunction with CC is as effective as the conventional long-course (at least four weeks) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile women with polycystic ovary syndrome.

OBJECTIVES

To determine the effectiveness of short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC with regard to ovulation and achievement of pregnancy in infertile women with PCOS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC to achieve ovulation or pregnancy in infertile women with PCOS.

Quasi-randomised controlled trials were not included in this review. Crossover trials were also excluded, as the design is not valid in this context.

Types of participants

Women of reproductive age (between 15 and 45 years) with anovulatory infertility attributed to PCOS.

Anovulation was defined as a lack of evidence of serum progesterone within the luteal range for the reference laboratory, menstrual cycles that were less frequent than every 35 days or fewer than six periods per year.

Infertility was defined as the inability to achieve pregnancy after one year of unprotected sexual intercourse.

PCOS was defined according to the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) criteria (ESHRE/ASRM 2003). Two of the following three manifestations were required for diagnosis of PCOS: (1) oligo or anovulation (menstrual cycles less frequent than every 35 days or fewer than six periods per year); (2) clinical or biochemical signs of hyperandrogenism, or both (clinical hirsutism or acne; or biochemical elevated testosterone, dehydroepiandrosterone, or androstenedione levels); and (3) polycystic ovary (ultrasound scanning showed enlarged ovary with peripheral cystic structures surrounded by an increased stromal mass)

Exclusion criteria

(1) Women with hyperprolactinaemia (greater than three times the upper limit of normal of the reporting laboratory's reference range), congenital adrenal hyperplasia (CAH) and Cushing's syndrome were excluded, since these conditions precluded the diagnosis of PCOS.

(2) Women diagnosed with hypogonadotropic hypogonadism (WHO group one anovulation) and ovarian failure (WHO group three anovulation) were also excluded from this review.

Types of interventions

Studies were eligible that compared short-course (less than four weeks) metformin plus CC versus long-course (four weeks or more) metformin plus CC.

Types of outcome measures

Primary outcomes

1. Live birth rate.

Secondary outcomes

2. Clinical pregnancy rate. Clinical pregnancy rate was defined as ultrasound evidence of gestational sac.

3. Ovulation rate (per woman). Ovulation was defined as mid luteal phase serum progesterone level greater than 3 ng/mL or in the luteal range for the reference laboratory or evidence of ovulation documented by ultrasound evaluation.

4. Multiple pregnancy rate.

5. Miscarriage rate (per pregnancy). Miscarriage was defined as the involuntary loss of pregnancy before 20 weeks of gestation.

6. Incidence of adverse effects (per woman). Adverse effects included gastro-intestinal disturbance, lactic acidosis, discontinuation of therapy, and other adverse effects described by the primary study authors.

Search methods for identification of studies

We searched for all published and unpublished RCTs of short-course versus long-course metformin plus CC, without language

restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

(1) We searched the Cochrane Menstrual Disorders & Subfertility Group trials register (inception to 1 February 2012). See Appendix 1; Cochrane Menstrual Disorders and Subfertility Group Specialised register search.
(2) We searched the Cochrane Central Register of Controlled Trials (inception to 1 February 2012) for keywords: Polycystic Ovary Syndrome (PCOS), metformin. See Appendix 2.
(3) We searched the following electronic databases for studies in all languages using following terms:
MEDLINE (inception to 1 February 2012). See Appendix 3.
CINAHL (1982 to 1 February 2012) database searched using comparable search terms to those used in MEDLINE.
EMBASE (inception to 1 February 2012). See Appendix 4.
PsycINFO (inception to 1 February 2012). See Appendix 5.

Searching other resources

Reference lists of included studies, other relevant review articles and textbooks were checked.
Pharmaceutical companies were contacted to locate any registered prospective clinical trials. Experts and specialists in the field were also contacted.

Data collection and analysis

A further update of this review is expected to be done in February 2014.

Selection of studies

Four review authors were involved. The search strategy described previously was employed to obtain titles, and where possible, abstracts of studies that were potentially relevant to the review. SS screened the titles and abstracts and discarded studies that were clearly ineligible but the aim was to be overly inclusive rather than risk losing relevant studies.
SS obtained copies of the full text articles and, after removing all information that could identify the authors, the publishers or the results of the study, the methods section were sent to the first review author (SS) and the second review author (BP). Both reviewers independently assessed whether the studies met the pre-stated inclusion criteria, with any disagreement resolved by discussion and final arbitration by the third review author (LP). Further information was sought from the primary study authors if papers contained insufficient information to make a decision about eligibility. The fourth review author (PP) was responsible for planning of analysis, data analysis, data interpretation and data presentation.

Data extraction and management

We planned to extract the following data from the studies included in the review:
General information
(a) Title
(b) Publication status
(c) Authors
(d) Contact address
(e) Country
(f) Resource
(g) Publication year
(h) Publication language
(i) Duplication of publishing
Trial Characteristics
(a) Randomization
(b) Allocation concealment
(c) Trial design: multi-centre or single centre; single phase or crossover design
(d) Blinding
(e) Number of patients randomised, excluded and analysed
(f) Source of funding
Baseline characteristics of the studied groups
(a) Definition and duration of pre-existing infertility
(b) Age of the patients
(c) Body mass index (BMI) of the patients
(d) Investigative work-up
(e) Other causes of infertility
(f) Previous administered treatment(s)

Intervention
(a) Type of intervention
(b) Duration of treatment with metformin
(c) Dose regimen
Outcomes
(a) Outcomes reported
(b) How are outcomes defined?
(c) How are outcomes measured?
(d) Timing of outcome measurement?
Two of the authors (SS and BP) were going to independently extract all data using data extraction forms designed according to Cochrane guidelines. We planned to pilot test the form designed with a sample of the studies to ensure that it was understandable, easy to complete and comprehensive. We planned to seek additional information on trial methodology from the authors of the trials which appeared to meet eligibility criteria but had aspects of methodology that were unclear. We planned that differences of opinion between the two review authors would be resolved by the third reviewer (LP). We planned to provide reasons for excluding

any trial.

Assessment of risk of bias in included studies

We planned that two review authors would independently assess the risk of bias of all studies that were eligible for the review with disagreement resolved by discussion or, if necessary, by the third review author. We would use the Cochrane risk of bias assessment tool (Higgins 2011) to assess: allocation (random sequence generation and allocation concealment); blinding of participants and personnel, blinding of outcome assessors; incomplete outcome data; selective reporting; and other bias.
It was intended that these assessments be used in investigation of any heterogeneity and in sensitivity analysis and to provide a context for discussing the reliability of the results.

Measures of treatment effect

We planned to express all dichotomous outcomes and results as odds ratios (OR) with 95% confidence intervals (CI). In order to perform meta-analysis using dichotomous data, we planned to extract the number in each of the two categories in each of the intervention groups (the numbers needed to be filled in the 2 x 2 table).

Unit of analysis issues

We planned that the primary analysis would be per woman randomised. Per pregnancy data would be included for the outcome of miscarriage. Data that did not allow valid analysis (e.g. "per cycle" data) would be briefly summarised in an additional table and would not be meta-analysed. Multiple live births (e.g. twins or triplets) would be counted as one live birth event.

Dealing with missing data

We planned to anlyse the data on an intention-to-treat basis as far as possible and attempts would be made to obtain missing data from the primary study authors. Where these were unobtainable, only the available data would be analysed.

Assessment of heterogeneity

We planned to consider whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary.
We planned that the data extracted from different trials would be assessed for heterogeneity by using several methods as follows:
1. Inspection of individual 95% confidence interval (CI) in the forest plots.
2. Using the Cochrane Q statistic. P-value of less than 0.10 would be used to indicate significant heterogeneity.
3. Calculating the I^2 statistic (Higgins 2003). A value of I^2 greater than 50% was planned to be used to indicate heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were ten or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We planned that if studies were clinically and statistically homogeneous, meta-analysis would be conducted using a fixed-effect model to calculate pooled ORs and 95% CIs.

Subgroup analysis and investigation of heterogeneity

If data were available, we planned to conduct subgroup analyses to determine the separate evidence within studies with participants' mean baseline BMI > 30 kg/m2 and those with participants' mean baseline BMI < 30 kg/m2.

Sensitivity analysis

We also intended performing sensitivity analysis in order to test the robustness of the review's conclusions by taking into account key decisions and assumptions that were made in the process of conducting the review. These approaches included the following.
1. Repeating the analysis excluding the trials most susceptible to bias based on the quality assessment (such as the trials with inadequate allocation concealment, high levels of post-randomization losses or exclusions).
2. Repeating the analysis, excluding the trials by using the following filters: publication language and country
3. Repeating the analysis using a random effects model.

Overall quality of the body of evidence: Summary of Findings Table

We planned to generate a Summary of Findings Table using GRADEPRO software. This table would evaluate the overall quality of the body of evidence for main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) would be justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

The search identified no potentially eligible studies.

Risk of bias in included studies

No studies were included in the review.

Effects of interventions

No studies were included inthe review.

DISCUSSION

We did not identify any randomised controlled trials that compared the effectiveness of short-course (less than four weeks) metformin plus clomiphene citrate versus long-course (four weeks or more) metformin plus clomiphene citrate in infertile women with PCOS. Nor did we identify any observational studies or case series assessing this comparison.

Among studies of borderline relevance, most used more than four weeks of metformin pretreatment before starting clomiphene citrate to induce ovulation in PCOS patients suffering from infertility. There were two studies (Hwu 2005; Khorram 2006) comparing short course metformin plus clomiphene citrate with clomiphene citrate alone. The study conducted by Khorram et al (Khorram 2006) used two weeks of metformin while the study reported by Hwu et al (Hwu 2005) gave 12 days of metformin pretreatment before beginning clomiphene citrate. Both studies found that short course metformin pretreatment resulted in improved response in relation to the control group (using clomiphene citrate alone) in terms of ovulation and pregnancy rates. Recent meta-analysis, however, revealed that addition of metformin to clomiphene citrate was effective in achieving live births while compared to clomiphene citrate alone only in women diagnosed with PCOS who were clomiphene-resistant (Moll 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Combination of metformin to clomiphene citrate has been proved to be more effective in achieving live births than clomiphene citrate alone in infertile women diagnosed with PCOS who are clomiphene-resistant. The optimal duration of metformin use before starting clomiphene citrate, however, is unknown. Recent studies have shown that short course (less than four weeks) metformin in conjunction with clomiphene citrate is more effective than clomiphene citrate alone for ovulation induction in clomiphene-resistant infertile women with PCOS. Prescribing short-course metformin before beginning clomiphene citrate should be beneficial to infertile women with PCOS. There are, however, no data from randomised controlled trials (or observational studies) to determine the effectiveness of short-course metformin as compared to the conventional long-course metformin pretreatment before initiation of clomiphene citrate.

Implications for research

Well-designed, randomised controlled trials are needed to evaluate the effectiveness of short-course metformin as compared to the conventional long-course metformin pretreatment in conjunction with clomiphene citrate for achievement of ovulation and pregnancy in women diagnosed with PCOS who are clomiphene-resistant.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MDSG Specialised register search

Menstrual Disorders and Subfertility (MDSG) specialised register search for SS1301 01.02.12
Keywords CONTAINS “polycystic ovary morphology”or “Polycystic Ovary Syndrome” or “PCOS” or Title CONTAINS “polycystic ovary morphology”or “Polycystic Ovary Syndrome” or “PCOS”
AND
Keywords CONTAINS “metformin” or Title CONTAINS “metformin”
AND
Keywords CONTAINS “*Clomiphene” or “clomiphene citrate” or Title CONTAINS “*Clomiphene” or “clomiphene citrate”

Appendix 2. CENTRAL search

1 exp Polycystic Ovary Syndrome/ (639)
2 PCOS.tw. (630)
3 PCOD.tw. (22)
4 stein-leventhal.tw. (3)
5 leventhal.tw. (8)
6 sclerocystic ovar$.tw. (0)
7 Polycystic Ovar$.tw. (935)
8 or/1-7 (1045)
9 (metformin and clomiphene).tw. (85)
10 (metformin and clomid).tw. (1)
11 (metformin and cc).tw. (31)
12 or/9-11 (88)
13 8 and 12 (84)

Appendix 3. MEDLINE search

1 exp Polycystic Ovary Syndrome/ (8750)
2 PCOS.tw. (4664)
3 PCOD.tw. (250)
4 stein-leventhal.tw. (569)
5 leventhal.tw. (654)
6 sclerocystic ovar$.tw. (80)
7 Polycystic Ovar$.tw. (8602)
8 or/1-7 (10964)
9 (metformin and clomiphene).tw. (161)
10 (metformin and clomid).tw. (2)
11 (metformin and cc).tw. (77)
12 or/9-11 (179)
13 8 and 12 (162)
14 short.tw. (438274)

15 long.tw. (831993)
16 week$.tw. (717685)
17 day$.tw. (1225889)
18 course.tw. (371989)
19 short-term.tw. (118532)
20 long-term.tw. (441889)
21 or/14-20 (2918138)
22 13 and 21 (72)
23 randomized controlled trial.pt. (318612)
24 controlled clinical trial.pt. (83402)
25 randomized.ab. (234424)
26 placebo.tw. (136137)
27 clinical trials as topic.sh. (157374)
28 randomly.ab. (172534)
29 trial.ti. (100307)
30 (crossover or cross-over or cross over).tw. (52100)
31 or/23-30 (780572)
32 exp animals/ not humans.sh. (3647344)
33 31 not 32 (720561)
34 22 and 33 (48)

Appendix 4. EMBASE search

1 (metformin and clomiphene).tw. (230)
2 (metformin and clomid).tw. (17)
3 (metformin and cc).tw. (110)
4 or/1-3 (263)
5 exp ovary polycystic disease/ (13700)
6 Polycystic Ovar$.tw. (10641)
7 PCOS.tw. (6118)
8 PCOD.tw. (297)
9 stein-leventhal.tw. (534)
10 leventhal.tw. (647)
11 sclerocystic ovar$.tw. (80)
12 or/5-11 (15409)
13 4 and 12 (234)
14 short.tw. (494843)
15 long.tw. (953330)
16 week$.tw. (846348)
17 day$.tw. (1424895)
18 course.tw. (428679)
19 short-term.tw. (137045)
20 long-term.tw. (526946)
21 or/14-20 (3351122)
22 13 and 21 (108)
23 trial.ti. (120389)
24 Clinical Trial/ (823603)
25 Randomized Controlled Trial/ (296357)
26 exp randomization/ (55579)
27 Single Blind Procedure/ (14735)
28 Double Blind Procedure/ (102763)
29 Crossover Procedure/ (31733)

30 Placebo/ (191694)
31 Randomi?ed controlled trial$.tw. (68283)
32 Rct.tw. (8403)
33 random allocation.tw. (1087)
34 randomly allocated.tw. (16142)
35 allocated randomly.tw. (1728)
36 (allocated adj2 random).tw. (691)
37 Single blind$.tw. (11480)
38 Double blind$.tw. (120977)
39 ((treble or triple) adj blind$).tw. (256)
40 placebo$.tw. (164540)
41 prospective study/ (181244)
42 or/24-41 (1171442)
43 case study/ (14547)
44 case report.tw. (213228)
45 abstract report/ or letter/ (806112)
46 or/43-45 (1029684)
47 42 not 46 (1137623)
48 22 and 47 (74)

Appendix 5. PsycINFO

1 (metformin and clomiphene).tw. (0)
2 (metformin and clomid).tw. (0)
3 (metformin and cc).tw. (0)
4 or/1-3 (0)
5 exp ovary polycystic disease/ (0)
6 Polycystic Ovar$.tw. (206)
7 PCOS.tw. (116)
8 PCOD.tw. (5)
9 stein-leventhal.tw. (2)
10 leventhal.tw. (220)
11 sclerocystic ovar$.tw. (1)
12 or/5-11 (447)
13 4 and 12 (0)

WHAT'S NEW

Last assessed as up-to-date: 1 February 2012.

Date	Event	Description
15 November 2012	Review declared as stable	As no studies are expected, this review will no longer be updated

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 1, 2008

Date	Event	Description
12 September 2012	New citation required but conclusions have not changed	No studies found for inclusion.
1 February 2012	New search has been performed	Search and methods updated. No studies found. Review has no included studies
26 May 2008	Amended	Converted to new review format.
28 September 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Supat Sinawat: screened potentially relevant studies, obtained titles and abstracts of potentially relevant studies, assessed the eligibility of studies to be included in the review, and wrote the review.

Pranom Buppasiri: assessed eligibility of studies to be included in the review, and approved the final version of the review.

Pisake Lumbiganon: making final decision about eligibility of the studies to be included in the review and wrote the review.

Porjai Pattanittum: commented and approved the final version of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.

External sources

- Thailand Research Fund, Thailand.
- Thai Cochrane Network, Thailand.

INDEX TERMS

Medical Subject Headings (MeSH)

Clomiphene [*administration & dosage]; Drug Administration Schedule; Drug Therapy, Combination [methods]; Fertility Agents, Female [*administration & dosage]; Infertility, Female [drug therapy]; Metformin [*administration & dosage]; Ovulation Induction [*methods]; Polycystic Ovary Syndrome [*complications]

MeSH check words

Female; Humans