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Statins for women with polycystic ovary syndrome not actively trying to conceive (Review)

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[Intervention Review]

Statins for women with polycystic ovary syndrome not actively trying to conceive

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ABSTRACT

Background

Statins are lipid-lowering agents with pleiotropic actions. Experts have proposed that in addition to improving the dyslipidaemia associated with polycystic ovary syndrome (PCOS), statins may also exert other beneficial metabolic and endocrine effects, such as reducing testosterone levels. This is an update of a Cochrane Review first published in 2011.

Objectives

To assess the efficacy and safety of statin therapy in women with PCOS who are not actively trying to conceive.

Search methods

We searched the Cochrane Gynaecology and Fertility Group specialised register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHLs, and four ongoing trials registers on 7 November 2022. We also handsearched relevant conference proceedings and the reference lists of relevant trials for any additional studies, and we contacted experts in the field for any further ongoing studies.

Selection criteria

We included randomised controlled trials (RCTs) that evaluated the effects of statin therapy in women with PCOS not actively trying to conceive. Eligible comparisons were statin versus placebo or no treatment, statin plus another agent versus the other agent alone, and statin versus another agent. We performed statistical analysis using Review Manager 5, and we assessed the certainty of the evidence using GRADE methods.

Data collection and analysis

We used standard Cochrane methodology. Our primary outcomes were resumption of menstrual regularity and resumption of spontaneous ovulation. Our secondary outcomes were clinical and physiological measures including hirsutism, acne severity, testosterone levels, and adverse events.

Main results

Six RCTs fulfilled the criteria for inclusion. They included 396 women with PCOS who received six weeks, three months, or six months of treatment; 374 women completed the studies. Three studies evaluated the effects of simvastatin and three studies evaluated the effects of atorvastatin. We summarised the results of the studies under the following comparisons.

Statins versus placebo (3 RCTs)

One trial measured resumption of menstrual regularity as menstrual cycle length in days. We are uncertain if statins compared with placebo shorten the mean length of the menstrual cycle (mean difference (MD) −2.00 days, 95% confidence interval (CI) −24.86 to 20.86; 37 participants; very low-certainty evidence). No studies reported resumption of spontaneous ovulation, improvement in hirsutism, or improvement in acne.

We are uncertain if statins compared with placebo reduce testosterone levels after six weeks (MD 0.06, 95% CI −0.72 to 0.84; 1 RCT, 20 participants; very low-certainty evidence), after 3 months (MD −0.53, 95% CI −1.61 to 0.54; 2 RCTs, 64 participants; very low-certainty evidence), or after 6 months (MD 0.10, 95% CI −0.43 to 0.63; 1 RCT, 28 participants; very low-certainty evidence)

Two studies recorded adverse events, and neither reported significant differences between the groups.

Statins plus metformin versus metformin alone (1 RCT)

The single RCT included in this comparison measured resumption of menstrual regularity as the number of spontaneous menses per six months. We are uncertain if statins plus metformin compared with metformin improves resumption of menstrual regularity (MD 0.60 menses, 95% CI 0.08 to 1.12; 69 participants; very low-certainty evidence). The study did not report resumption of spontaneous ovulation.

We are uncertain if statins plus metformin compared with metformin alone improves hirsutism measured using the Ferriman-Gallwey score (MD −0.16, 95% CI −0.91 to 0.59; 69 participants; very low-certainty evidence), acne severity measured on a scale of 0 to 3 (MD −0.31, 95% CI −0.67 to 0.05; 69 participants; very low-certainty evidence), or testosterone levels (MD −0.03, 95% CI −0.37 to 0.31; 69 participants; very low-certainty evidence). The study reported that no significant adverse events occurred.

Statins plus oral contraceptive pill versus oral contraceptive pill alone (1 RCT)

The single RCT included in this comparison did not report resumption of menstrual regularity or spontaneous ovulation. We are uncertain if statins plus the oral contraceptive pill (OCP) improves hirsutism compared with OCP alone (MD −0.12, 95% CI −0.41 to 0.17; 48 participants; very low-certainty evidence). The study did not report improvement in acne severity. We are also uncertain if statins plus OCP compared with OCP alone reduces testosterone levels, because the certainty of the evidence was very low (MD −0.82, 95% CI −1.38 to −0.26; 48 participants). The study reported that no participants experienced significant side effects.

Statins versus metformin (2 RCTs)

We are uncertain if statins improve menstrual regularity compared with metformin (number of spontaneous menses per six months) compared to metformin (MD 0.50 menses, 95% CI −0.05 to 1.05; 1 RCT, 61 participants, very low-certainty evidence). No studies reported resumption of spontaneous ovulation.

We are uncertain if statins compared with metformin reduce hirsutism measured using the Ferriman-Gallwey score (MD −0.26, 95% CI −0.97 to 0.45; 1 RCT, 61 participants; very low-certainty evidence), acne severity measured on a scale of 0 to 3 (MD −0.18, 95% CI −0.53 to 0.17; 1 RCT, 61 participants; very low-certainty evidence), or testosterone levels (MD −0.24, 95% CI −0.58 to 0.10; 1 RCT, 61 participants; very low-certainty evidence).

Both trials reported that no significant adverse events had occurred.

Statins versus oral contraceptive pill plus flutamide (1 RCT)

According to the study report, no participants experienced any significant side effects. There were no available data for any other main outcomes.

Authors' conclusions

The evidence for all main outcomes of this review was of very low certainty. Due to the limited evidence, we are uncertain if statins compared with placebo, or statins plus metformin compared with metformin alone, improve resumption of menstrual regularity. The trial evaluating statin plus OCP versus OCP alone reported neither of our primary outcomes. No other studies reported resumption of spontaneous ovulation. We are uncertain if statins improve hirsutism, acne severity, or testosterone. All trials that measured adverse events reported no significant differences between the groups.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of statins for women with polycystic ovary syndrome who are not trying to get pregnant?

Key messages

1. We are uncertain if statins improve the regularity of menstrual periods, hirsutism (excessive hair growth), acne (pimples), or levels of testosterone (male sex hormone).
2. No studies looked at spontaneous ovulation.
3. Statins may not increase the risk of unwanted events, though the evidence is limited.

What is polycystic ovary syndrome?

Women with polycystic ovary syndrome (PCOS) may suffer from irregular periods, hirsutism (excessive hair growth on body areas where hair typically grown on men, including the face, chest, and back), and acne (pimples) because of androgen excess (high levels of male hormones). This condition can affect women of any age, but is most common in those who have menstrual periods.

How can polycystic ovary syndrome be treated?

Statins are medicines that help lower the levels of 'bad' lipids (fats) in the blood to prevent heart disease; they may also prevent other metabolic conditions. High levels of male hormones (testosterone) is one of the most prominent features of PCOS. This is called androgen excess, and it is associated with several metabolic disorders such as insulin resistance, diabetes, and increased risk of heart disease. Therefore, reducing the level of male hormones could be beneficial for women with PCOS. Statins may interfere with male hormone production, but it is unclear whether they can directly reduce testosterone levels. Long-term use of statins may have risks. Therefore, it is important to evaluate the benefits and risks of statins in women with PCOS.

What did we want to find out?

We wanted to know whether any type of statin has benefits for women with PCOS who are not actively trying to get pregnant. We were interested in the effect of statins on:

1. increasing the regularity of menstrual cycles and ovulation; and
2. reducing hair excess, acne, and testosterone levels.

We also wanted to know if statins have any unwanted effects. This is an update of a review first published in 2011.

What did we do?

We searched for studies that evaluated statins compared with placebo (dummy treatment), no treatment, or another medicine, in women with PCOS who were not trying to get pregnant. We were only interested in studies that allocated each woman to one or another treatment at random. This type of study usually provides the most reliable evidence about the effects of a treatment. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We included six studies that enrolled a total of 396 women. Four studies were conducted in Europe (265 women), one in the USA (20 women), and one in Iran (111 women). Pharmaceutical companies funded three studies.

Main results

We are uncertain if statins compared with placebo, or statins plus metformin compared with metformin alone, improve the regularity of menstrual periods. No studies reported resumption of ovulation. We are uncertain if statins improve hirsutism, acne, or testosterone levels. All the studies that recorded unwanted effects found no clear differences in unwanted effects between the group of women taking statins and the other treatment group.

What are the limitations of the evidence?

We included very few studies, most of which enrolled few women, and the results were very inconsistent across studies. For these reasons, we have very little confidence in the evidence.

How up to date is this evidence?

The evidence is current up to 7 November 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Statin compared to placebo for women with polycystic ovary syndrome not actively trying to conceive

Statin compared to placebo for women with polycystic ovary syndrome not actively trying to conceive

Patient or population: women with polycystic ovary syndrome not actively trying to conceive
Setting: clinic
Intervention: statin
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
		Risk with placebo	Risk with statin		
Resumption of menstrual regularity (menstrual cycle length in days)		The mean menstrual cycle length was 52 days.	MD 2 days fewer (24.86 fewer to 20.86 more)	37 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Resumption of spontaneous ovulation		No studies reported spontaneous ovulation.			
Improvement in hirsutism		No studies reported hirsutism.			
Improvement in acne severity		No studies reported acne severity.			
Improvement in testosterone level (nmol/L)	After 6 weeks' treatment	The mean change in testosterone level after 6 weeks' treatment was −0.58 nmol/L.	MD 0.06 nmol/L higher (0.72 lower to 0.84 higher)	20 (1 study)	⊕⊖⊖⊖ **Very low**[a]
	After 3 months' treatment	The mean change in testosterone level (nmol/L) after 3 months' treatment was −0.1 nmol/L.	MD 0.53 nmol/L lower (1.61 lower to 0.54 higher)	65 (2 studies)	⊕⊖⊖⊖ **Very low**[a]
	After 6 months' treatment	The mean change in testosterone level (nmol/L) after 6 months' treatment was −0.2 nmol/L.	MD 0.10 nmol/L higher (0.43 lower to 0.63 higher)	28 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Adverse effects		2 studies assessed adverse events and neither reported a significant difference between the groups.[b]			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded twice for very serious imprecision (wide CI, small sample size) and once for risk of bias.
[b] One woman in the statin group stopped the treatment for arthralgia in Puurunen 2013. No adverse events were observed in either group in Sathyapalan 2009. Raja-Khan 2011 did not report adverse events.

Summary of findings 2. Statin plus metformin compared to metformin alone for women with polycystic ovary syndrome not actively trying to conceive

Statin plus metformin compared to metformin alone for women with polycystic ovary syndrome not actively trying to conceive

Patient or population: women with polycystic ovary syndrome not actively trying to conceive
Setting: clinic
Intervention: statin + metformin
Comparison: metformin alone

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with metformin	Risk with statin + metformin		
Resumption of menstrual regularity (spontaneous menses per 6 months)	The mean number of spontaneous menses per 6 months was 1.1.	MD 0.6 menses more (0.08 fewer to 1.12 more)	69 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Resumption of spontaneous ovulation	Banaszewska 2011 did not report spontaneous ovulation.			
Improvement in hirsutism (Ferriman-Gallwey score) after 6 months' treatment	The mean change in hirsutism after 6 months' treatment was −0.84.	MD 0.16 lower (0.91 lower to 0.59 higher)	69 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Improvement in acne severity (scale of 0–3) after 6 months' treatment	The mean change in acne severity after 6 months' treatment was −0.75.	MD 0.31 lower (0.67 lower to 0.05 higher)	69 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Improvement in testosterone level (nmol/L) after 6 months' treatment	The mean change in testosterone level after 6 months' treatment was −0.52 nmol/L.	MD 0.03 nmol/L lower (0.37 lower to 0.31 lower)	69 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Adverse effects	Banaszewska 2011 reported that no significant adverse events had occurred.			

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded twice for very serious imprecision (wide CI, small sample size, single study) and twice for very serious risk of bias concerns.

Summary of findings 3. Statin plus oral contraceptive pill compared to oral contraceptive pill alone for women with polycystic ovary syndrome not actively trying to conceive

Statin plus OCP compared to OCP for women with polycystic ovary syndrome not actively trying to conceive

Patient or population: women with polycystic ovary syndrome not actively trying to conceive
Setting: clinic
Intervention: statin + OCP
Comparison: OCP

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with OCP	Risk with statin + OCP		
Resumption of menstrual regularity	Duleba 2006 did not report resumption of menstrual regularity.			
Resumption of spontaneous ovulation	Duleba 2006 did not report on resumption of spontaneous ovulation.			
Improvement in hirsutism (Ferriman-Gallwey score)	The mean change in hirsutism was −0.13.	MD 0.12 lower (0.41 lower to 0.17 higher)	48 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Improvement in acne severity	Duleba 2006 did not report acne severity.			
Testosterone level (change from baseline in nmol/L)	The mean change in testosterone level (nmol/L) was −0.38 nmol/L.	MD 0.82 nmol/L lower (1.38 lower to 0.26 lower)	48 (1 study)	⊕⊖⊖⊖ **Very low**[a]
Adverse effects	Duleba 2006 reported that no significant adverse events occurred.			

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OCP:** oral contraceptive pill.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded twice for very serious imprecision (wide CI, small sample size, single study) and twice for very serious risk of bias concerns.

Summary of findings 4. Statin compared to metformin for women with polycystic ovary syndrome not actively trying to conceive

Statin compared to metformin for women with polycystic ovary syndrome not actively trying to conceive

Patient or population: women with polycystic ovary syndrome not actively trying to conceive
Setting: clinic
Intervention: statin
Comparison: metformin

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with metformin	Risk with statin		
Resumption of menstrual regularity (number of spontaneous menses per 6 months) after 6 months' treatment	The mean number of spontaneous menses per 6 months after 6 months' treatment was 1.1	MD 0.5 menses more (0.05 more to 1.05 more)	61 (1 study)	⊕⊝⊝⊝ **Very low**[a]
Resumption of spontaneous ovulation	No studies reported resumption of spontaneous ovulation.			
Improvement in hirsutism (Ferriman-Gallwey score) after 6 months' treatment	The mean change in hirsutism after 6 months' treatment was −0.84.	MD 0.26 lower (0.97 lower to 0.45 higher)	61 (1 study)	⊕⊝⊝⊝ **Very low**[a]
Improvement in acne severity (scale of 0–3) after 6 months' treatment	The mean change in acne score after 6 months' treatment was −0.75.	MD 0.18 lower (0.53 lower to 0.17 higher)	61 (1 study)	⊕⊝⊝⊝ **Very low**[a]
Improvement in testosterone level (nmol/L) after 6 months' treatment	The mean change in testosterone level after 6 months' treatment was −0.52 nmol/L.	MD 0.24 nmol/L lower (0.58 lower to 0.1 higher)	61 (1 study)	⊕⊝⊝⊝ **Very low**[a]
Adverse effects	The studies reported that no significant adverse events had occurred.[b]			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded twice for very serious imprecision (wide CI, small sample size, single study) and twice for very serious risk of bias concerns.
[b]Banaszewska 2011 reported that six subjects using metformin experienced transient gastrointestinal side effects including diarrhoea; however, these side effects did not result in discontinuation of treatment. Mehrabian 2016 reported that no participants experienced significant side effects.

Summary of findings 5. Statin compared to oral contraceptive pill plus flutamide for women with polycystic ovary syndrome not actively trying to conceive

Statin compared to OCP plus flutamide for women with polycystic ovary syndrome not actively trying to conceive

Patient or population: women with polycystic ovary syndrome not actively trying to conceive
Setting: clinic
Intervention: statin
Comparison: OCP plus flutamide

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with OCP alone or in combination with another agent	Risk with statin		
Resumption of menstrual regularity	Mehrabian 2016 did not report resumption of menstrual regularity.			
Resumption of spontaneous ovulation	Mehrabian 2016 did not report resumption of spontaneous ovulation.			
Improvement in hirsutism	Mehrabian 2016 did not report hirsutism.			
Improvement in acne severity	Mehrabian 2016 did not report acne severity.			
Improvement in testosterone level.	Mehrabian 2016 did not report testosterone levels.			
Adverse effects	Mehrabian 2016 reported that no women experienced any significant side effects.			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval;**OCP:** oral contraceptive pill.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

BACKGROUND

Description of the condition

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a reported prevalence of 5% to 20% depending on the population studied and definitions used (Azziz 2016; Bozdag 2016; Fauser 2012; Teede 2018). The clinical expression of PCOS varies but commonly includes oligo-ovulation or anovulation, hyperandrogenism, and the presence of polycystic ovaries. According to the Rotterdam criteria, women must meet at least two of the following three criteria to receive a PCOS diagnosis (ESHRE/ASRM 2004).

1. Oligo-ovulation or anovulation (infrequent or no ovulation)
2. Clinical or biochemical signs of hyperandrogenism (elevated levels of androgens)
3. Polycystic ovaries on ultrasound

In addition, the diagnosing clinician must rule out other causes for hyperandrogenism (e.g. congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumours).

Clinical and biochemical hyperandrogenism are prominent features in women with PCOS (Escobar-Morreale 2018; Goodman 2015; Sharma 2021; Teede 2018), with a reported prevalence of 60% to 80% (Chin 2021; Spritzer 2016). Clinical features of hyperandrogenism include hirsutism (excess male-pattern hair growth), acne, and androgenetic alopecia (Escobar-Morreale 2018; Franik 2018; Garzia 2022). Androgen excess represents an independent risk factor for development of hypertension and increased cardiovascular risk in women with PCOS (Azziz 2016; Barrea 2021), and it can worsen metabolic disorders such as obesity, insulin resistance, and glucose intolerance in this population (Dumesic 2020; Gilbert 2018). These metabolic disorders are involved in both the pathogenesis and the progression of the disease (Armanini 2022; Azziz 2016; Ding 2021; Ezeh 2022; Rosenfield 2016; Sanchez-Garrido 2020). Obesity and severe acne vulgaris can also lead to psychological sequelae (Damone 2019; Kolhe 2022). Thus, hyperandrogenism is one main target for treatment to improve quality of life and decrease morbidity.

Over the longer term, PCOS is associated with a broad range of adverse sequelae, including dyslipidaemia (abnormal lipid levels in the blood), hypertension, insulin resistance with compensatory hyperinsulinaemia, gestational diabetes, and type 2 diabetes mellitus (Azziz 2016; Cooney 2018; Doherty 2015). Experts believe than women with PCOS have an increased cardiovascular risk, mediated mostly by insulin resistance, as well as by hormonal and metabolic processes (Azziz 2018; Hart 2015; Osibogun 2020; Wekker 2020). Chronic low-grade inflammation, such as increased white blood cell count and high levels of C-reactive protein (CRP) may also be associated with long-term metabolic complications and high cardiovascular risk (Osibogun 2020; Rudnicka 2021). The effect of menopausal transition on the long-term health consequences of PCOS is mostly uncertain, owing to limited evidence. The PCOS phenotype of affected women improves with ageing (Mukta 2022; Mumusoglu 2019). Therefore, the differences in the cardiometabolic risk profiles between women with PCOS and the general population seem to decrease after menopause.

Description of the intervention

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (or statins, such as atorvastatin and simvastatin) are amongst the most prescribed drugs in the world. Statins are prescribed for dyslipidaemia because they lower total cholesterol and low-density lipoprotein (LDL) cholesterol levels (Adams 2015). Research has attributed the effects of statins to reduced cholesterol biosynthesis through competitive inhibition of HMG-CoA reductase, which converts HMG-CoA to L-mevalonate. Statin therapy reduces the risk of all-cause mortality and cardiovascular events (such as myocardial infarction and stroke) in adults at increased cardiovascular risk (Chou 2022).

How the intervention might work

Statins inhibit the synthesis of mevalonate (the key precursor to cholesterol biosynthesis) and ultimately inhibit androgen synthesis. Steroidogenesis within the ovary begins in the theca cell. Lipoprotein receptors on the cell surface, for high-density lipoprotein (HDL) and LDL, transport cholesterol into the cell to act as the substrate for steroid synthesis. Steroid synthesis within the theca cell begins with synthesis of the androgen androstenedione, which then may be converted to oestrogen by aromatisation within the granulosa cells, or to testosterone by reductases. Modification though increased or decreased availability of lipoprotein to the theca cell receptors can augment or decrease subsequent androgen synthesis (Schiffer 2019). Since statins decrease the availability of cholesterol (an essential substrate for testosterone production), they may reduce serum testosterone levels. Elevated testosterone is one important factor that inhibits ovulation and leads to menstrual disorders in PCOS. Therefore, statins may benefit women with PCOS who have hyperandrogenism, by restoring ovulation and regulating menstrual cycles.

Moreover, according to several studies, statins have immunomodulatory properties with potential beneficial effects beyond their lipid-lowering properties (Oesterle 2017; Sheridan 2022; Zeiser 2018). Data from clinical trials have demonstrated that statin therapy leads to a decrease in the level of the inflammatory marker CRP (Plenge 2002; Ridker 2005).

Why it is important to do this review

PCOS is a complex endocrine condition. The international evidence-based guideline for the assessment and management of PCOS acknowledges that women with this condition have increased cardiovascular disease risk factors, though good evidence from clinical trials is lacking (ACOG 2018; Teede 2018). Furthermore, long-term statin use has been linked to an increased risk of type 2 diabetes (Crandall 2017). This is an update of a Cochrane Review published in 2011 (Raval 2011). Several new studies evaluating statins in PCOS have been published since the last version of this review. There is a need to determine any potential beneficial or harmful effects of statins, alone or in combination with other agents, on metabolic and hormonal variables affecting clinical outcomes in women with PCOS. This may have implications for treatment of common presenting features of the condition.

OBJECTIVES

To assess the efficacy and safety of statin therapy in women with polycystic ovary syndrome who are not actively trying to conceive.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that evaluated any statin (e.g. atorvastatin, simvastatin, pravastatin, rosuvastatin) versus placebo, no treatment, or another drug; or any statin in combination with another drug versus the other drug alone. We excluded quasi- or pseudo-RCTs. Cross-over trials were eligible, but we only used data from the first phase (before cross-over).

Types of participants

We included studies of women with PCOS who were not actively trying to conceive, as statins are contraindicated in pregnancy. Eligible criteria for PCOS diagnosis were the European Society for Human Reproduction and Embryology (ESHRE)- and American Society for Reproductive Medicine (ASRM)-sponsored PCOS Consensus Workshop criteria (the Rotterdam criteria; ESHRE/ASRM 2004; Rotterdam 2004) or the US National Institutes of Health (NIH) consensus criteria (Zawadzki 1992).

If the study report did not clearly state the diagnostic criteria, we contacted the study authors for clarification. If this information was unavailable, we excluded the study. Changes in diagnostic criteria might produce variability in the clinical characteristics of the women included in the studies and the results obtained. We planned to consider, document, and explore these changes in a sensitivity analysis.

Types of interventions

The following comparisons were eligible for this review.

1. Statin versus placebo or no treatment
2. Statin plus another agent versus the other agent alone
3. Statin versus another agent

Types of outcome measures

Primary outcomes

1. Resumption of menstrual regularity (i.e. initiation of menses or significant shortening of cycles, number of women with resumption of normal menstrual cycle (between 21 and 34 days), or as defined by study authors).
2. Resumption of spontaneous ovulation documented by biochemical methods (i.e. evidence of serum progesterone in the luteal range for the reference laboratory; or rise in basal body temperature of more than 0.4 °C, as measured on a basal body temperature chart, for 10 days or more).

Secondary outcomes

1. Improvement in body composition
   a. Body mass index (BMI; kg/m^2; lower is better)
   b. Waist circumference (cm; lower is better)
   c. Waist-hip ratio (WHR; lower is better)
2. Improvement in hirsutism (Ferriman-Gallwey score; lower is better)
3. Improvement in acne severity (clinical score as reported by study authors)
4. Improvement in testosterone level (nmol/L; lower is better)
5. Improvement in lipid profile
   a. Total cholesterol (mmol/L; lower is better)
   b. LDL cholesterol (mmol/L; lower is better)
   c. HDL cholesterol (mmol/L; higher is better)
   d. Triglycerides (mmol/L; lower is better)
6. Improvement in high-sensitivity CRP (hs-CRP; nmol/L; lower is better)
7. Improvement in insulin sensitivity
   a. Fasting insulin (µIU/mL; lower is better)
   b. Glucose/insulin ratio (lower is better)
   c. Homeostatic model assessment for insulin resistance (HOMA-IR; lower is better)
   d. Standard measures from euglycaemic clamps or intravenous glucose tolerance tests
8. Adverse effects of statins: all serious and non-serious adverse events, especially rhabdomyolysis, creatinine kinase levels over 10 times the upper limit of normal values, and liver aminotransferase levels over three times the upper limit of normal values.

Search methods for identification of studies

We searched for all published and unpublished RCTs that evaluated statins in women with PCOS not actively trying to conceive, without language restriction, and in consultation with the Cochrane Gynaecology and Fertility (CGF) Group Information Specialist (Marian Showell).

Electronic searches

We searched the following electronic databases for relevant studies.

1. CGF Specialised Register of Controlled Trials, ProCite platform (searched 7 November 2022; Appendix 1)
2. CENTRAL via the Cochrane Register of Studies Online (CRSO), web platform (searched 7 November 2022; Appendix 2)
3. MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid platform (1946 to 7 November 2022; Appendix 3)
4. Embase, Ovid platform (1980 to 7 November 2022; Appendix 4)
5. PsycINFO, Ovid platform (1806 to 7 November 2022; Appendix 5)
6. CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature), EBSCO platform (1961 to 25 September 2019 (all later CINAHL references are included in the CENTRAL search output); Appendix 6)

We carried out initial searches to July 2011, then updated the searches in September 2019 and November 2022, with assistance from the CGF Group Information Specialist.

Searching other resources

We searched the following trials registers for ongoing trials.

1. NIH Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/)
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/)
3. CenterWatch Clinical Trials Listing Service (www.centerwatch.com/)
4. NIH Clinical Center: Search the Studies (clinicalstudies.info.nih.gov/)

We also checked the reference lists of relevant trials and systematic reviews retrieved by the search and contacted experts in the field to obtain additional data. We handsearched journals and conference proceedings not covered in the CGF register, in liaison with the CGF Information Specialist. Lastly, we searched Google Scholar for recent trials not yet indexed in the major databases.

Data collection and analysis

Selection of studies

Two review authors (TX and EK or EBK) independently screened the titles and abstracts of the records returned by the search and retrieved the full-text articles of all potentially relevant studies. The same two review authors independently assessed each of these studies for inclusion in the review using Covidence. We resolved any disagreements by discussion or by involving a third review author (EBK when the selection was made by TX and EK). We excluded studies that did not meet the eligibility criteria and recorded the reasons for exclusion in the Characteristics of excluded studies table.

We screened all potentially eligible studies using the checklist of the Pregnancy & Childbirth group (Alfirevic 2021). Any studies that had been registered and completed but not (yet) published, as well as potentially problematic studies according to the integrity checklist, were listed as awaiting classification (Studies awaiting classification).

Data extraction and management

Two review authors (TX and EF or EK) independently entered data into a data extraction form supplied by the Cochrane Gynaecology and Fertility Group. We collected data on study characteristics, including methods, participants, interventions, and outcomes. We resolved any disagreements by referring to the trial report and through discussion and consultation with a third author (MC). If data were missing from trial reports, or the reported data were insufficient, we contacted the trial authors for additional information. Where possible, we extracted data to allow an intention-to-treat (ITT) analysis (including all women in the groups to which they were originally randomly assigned). If the number randomised and the number analysed were inconsistent, we calculated the percentage loss to follow-up and reported this information in an additional table. The review authors were not blinded to the names of trialists, journals, or institutions. Table 1 shows the conversion factors used to make uniform units of the parameters.

Assessment of risk of bias in included studies

Two review authors (TX and EF or EK) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool (RoB 1), which covers the following domains (Higgins 2017).

1. Selection bias (random sequence generation and allocation concealment)
2. Performance bias (blinding of participants and personnel)
3. Detection bias (blinding of outcome assessors)
4. Attrition bias (incomplete outcome data)
5. Reporting bias (selective reporting)
6. Other potential sources of bias

We rated studies as being at high, low, or unclear risk of bias for each domain, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We assigned an 'unclear' judgement where trials provided insufficient detail, or the risk of bias was unknown, or the domain was irrelevant to the study. We resolved any disagreements by discussion with a third review author (EBK). We described all judgements fully and presented our conclusions in the Characteristics of included studies table.

Measures of treatment effect

We performed statistical analyses according to the statistical guidelines provided in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2022). For dichotomous outcomes, we planned to report the odds ratio (OR), together with its 95% confidence interval (CI). For continuous outcomes, we used the mean difference (MD) with its 95% CI.

Unit of analysis issues

We used data from only the first phase of cross-over trials (i.e. before cross-over). We excluded any cross-over trials that did not provide results at this time point.

Dealing with missing data

We contacted trial authors to obtain descriptive statistics on the outcomes of interest where necessary. In addition, if trial reports provided a narrative summary of an outcome measure (e.g. 'no difference in menstrual regularity') without the number of events, we recorded the summary in the Results section. We found no studies in which only a subset of participants was eligible for this review.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by calculating the I^2 statistic, considering an I^2 value greater than 50% to be indicative of substantial heterogeneity (Higgins 2022).

Assessment of reporting biases

Had we included more than 10 studies in a meta-analysis, we would have assessed publication bias by creating a funnel plot.

Data synthesis

Where there were sufficient data, we calculated a summary statistic for each outcome with respect to the interventions (as described in Types of interventions) using a fixed-effect model and RevMan 5.4.1 software (Review Manager 2020). In cases of substantial heterogeneity, we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore sources of heterogeneity (based on type of statin, type of comparison, duration of intervention, and ethnicity of participants).

Sensitivity analysis

We planned to conduct sensitivity analyses to examine the stability of the results in relation to several factors (including comedication,

quality of allocation concealment, blinding, ITT analysis, source of funding, different diagnostic criteria of PCOS, and obesity) if sufficient data were available.

We also planned sensitivity analyses restricted to studies with low risk of selection bias (random sequence generation and allocation concealment) for all primary outcomes.

Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables using GRADEpro software (GRADEpro GDT 2014), and we assessed the certainty of evidence using GRADE methodology (Ryan 2016; Schünemann 2013). The tables presented the overall certainty of the body of evidence for the main review outcomes (resumption of menstrual regularity, resumption of spontaneous ovulation, hirsutism, acne, testosterone levels, and adverse effects) for the main review comparisons (statin versus placebo or no treatment, statin plus another agent versus the other agent alone, statin versus another agent). Two review authors (TX and EK) independently assessed the certainty of the evidence as high, moderate, low, or very low based on the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias). We resolved any disagreements by discussion or by consulting a third review author (EBK). We provided justifications for the GRADE judgements in footnotes to the summary of findings tables.

RESULTS

Description of studies

See the Characteristics of included studies, Studies awaiting classification, and Characteristics of excluded studies tables.

Results of the search

The first version of this review included four trials. In the current update, we retrieved 244 records (after removal of duplicates), of which we discarded 206 during title and abstract screening. We then retrieved and assessed 38 full-text articles, excluding 18 (14 trials). Two new trials (five records) were eligible for inclusion. We identified seven additional records of previously included studies. Eight trials are awaiting classification. Figure 1 shows the study selection process in a PRISMA flow diagram.

Figure 1.

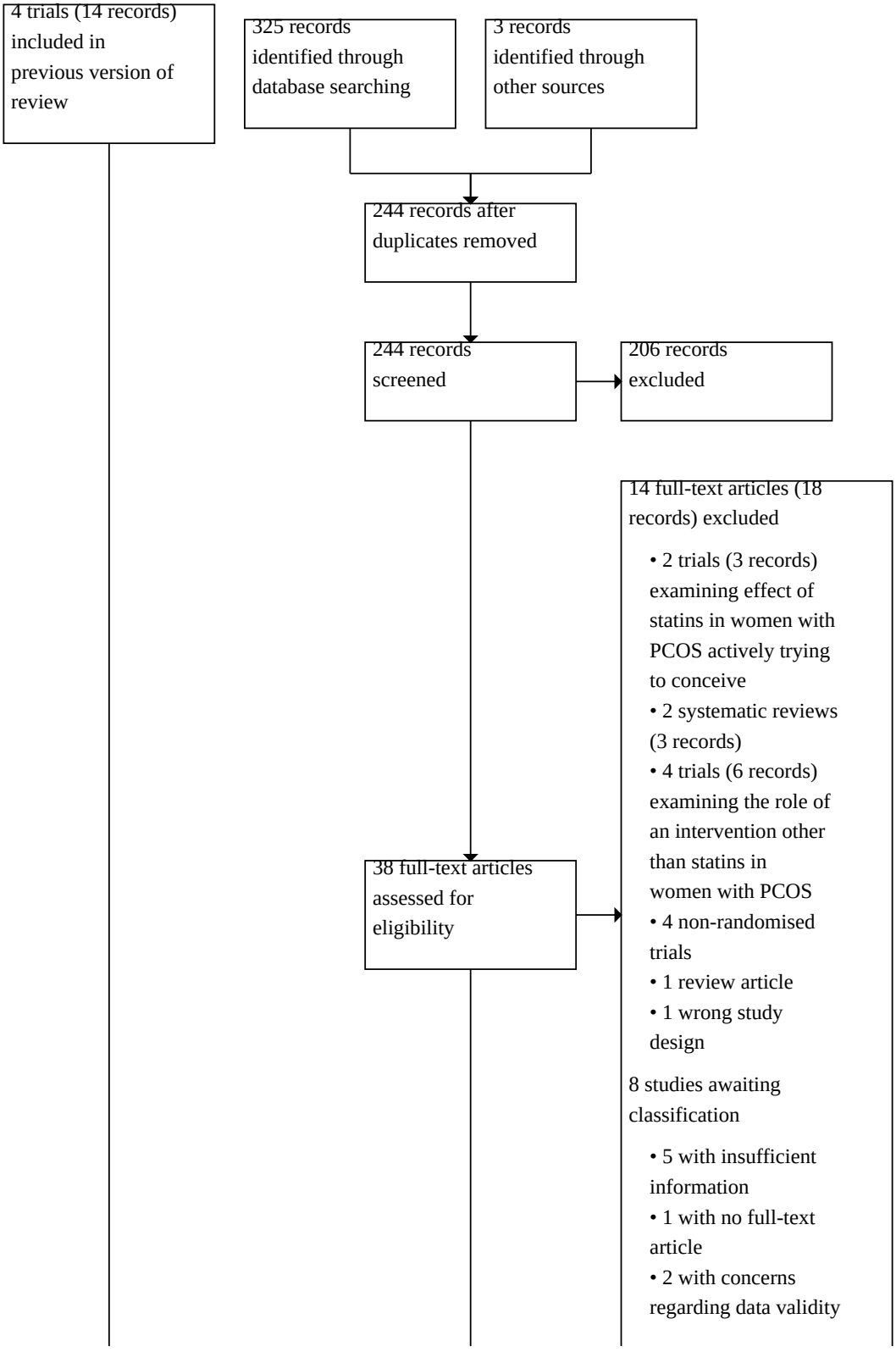
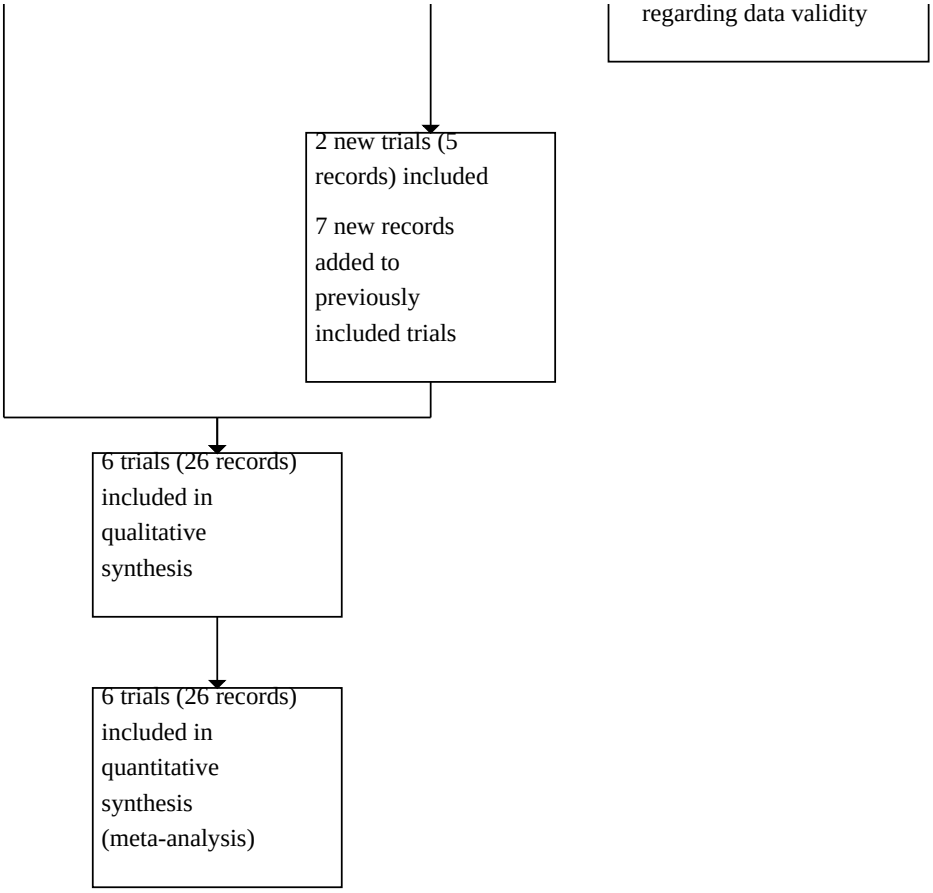


Figure 1. (Continued)



Included studies

We included six RCTs: two identified in this update (Mehrabian 2016; Puurunen 2013) and four from the previous version of the review (Banaszewska 2011; Duleba 2006; Raja-Khan 2011; Sathyapalan 2009).

Design, setting, and funding

Five RCTs had a parallel-group design, and Duleba 2006 had a cross-over design (we included the data from the first phase, before cross-over). Sample sizes ranged from 20 to 139 women. All studies were single-centre RCTs. Four took place in European countries (Banaszewska 2011; Duleba 2006; Puurunen 2013; Sathyapalan 2009), one in the USA (Raja-Khan 2011), and one in Iran (Mehrabian 2016). All participants were recruited within university-associated medical centres or hospitals.

Pharmaceutical companies provided the study drugs for five studies (Banaszewska 2011; Duleba 2006; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009). Banaszewska 2011 was supported by the Polish State Committee for Scientific Research and the National Institute of Child Health and Human Development (NICHD); Duleba 2006 was supported by an NIH grant; Puurunen 2013 by the Academy of Finland and other funding bodies; Raja-Khan 2011 by an NIH grant, NICHD, a construction grant to Pennsylvania State University, and a research grant from Pfizer; and Sathyapalan 2009 by an unrestricted grant from the pharmaceutical company Pfizer. Mehrabian 2016 received institutional funding.

Participants

A total of 396 women were randomised to either statin treatment, placebo, or active control, and 374 women completed the studies. A total of 265 women took part in the European studies, 20 in the USA study, and 111 in the Iranian study. Only Mehrabian 2016 stated age as an inclusion criterion. Duleba 2006 had the youngest participants (mean age 23.9 years), and Puurunen 2013 had the oldest participants (mean age 39 years). The mean BMI of participants was in the normal range (20 kg/m^2 to 25 kg/m^2) in two studies (Banaszewska 2011; Duleba 2006), and in the overweight or obese range (more than 25 kg/m^2) in the remaining studies. The mean baseline total serum testosterone levels were highest in Sathyapalan 2009 (mean 4.1 nmol/L to 4.4 nmol/L) and lowest in Puurunen 2013 (mean 0.9 nmol/L to 1.4 nmol/L). In Puurunen 2013 and Raja-Khan 2011, baseline mean testosterone levels differed between the study arms. See Table 2 for details.

Regarding baseline PCOS criteria, Banaszewska 2011 reported that 79% of women had significant hirsutism, and 85% had oligomenorrhoea.

All the studies provided the diagnostic criteria for PCOS. The main components of diagnostic criteria were as follows.

1. Clinical or biochemical signs of hyperandrogenism
2. Oligo-ovulation or anovulation
3. Polycystic ovaries

Sathyapalan 2009 included women with all three components; Duleba 2006 included women with any two of the three components, as per the internationally agreed definition of PCOS (ESHRE/ASRM 2004); and Banaszewska 2011 and Puurunen 2013 included women who met the modified Rotterdam criteria (the first component plus either of the other two components). Mehrabian 2016 and Raja-Khan 2011 included women with PCOS defined using the 1990 NIH criteria. Mehrabian 2016 included only unmarried women.

All the studies confirmed absence of non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, and androgen-secreting tumours. Raja-Khan 2011 included women with PCOS who had LDL cholesterol levels above 100 mg/dL. The remaining studies provided no data on comorbidities. Raja-Khan 2011 reported use of the oral contraceptive pill (OCP) by one woman in the statin group and use of antihypertensives by one woman in each of the two groups. In addition, no participants in Raja-Khan 2011 used metformin or other medication that could affect outcomes. Sathyapalan 2009 evaluated therapy-naive women, and the remaining studies provided no details about previous medication. However, Banaszewska 2011, Duleba 2006, and Puurunen 2013 required that all participants refrain from using any form of oral contraceptives, other steroid hormones, and any other treatments likely to affect ovarian function, insulin sensitivity, or lipid profile three months before enrolment. Raja-Khan 2011 provided no details about treatment before the study.

All studies excluded women who were using sex hormones or drugs known to affect lipid metabolism, ovarian function, or insulin sensitivity. Four studies excluded women with type 2 diabetes mellitus or thyroid disease (Banaszewska 2011; Duleba 2006; Puurunen 2013; Raja-Khan 2011). In addition, Raja-Khan 2011 excluded women with active liver disease or thyroid disease, and woman who were pregnant or breastfeeding. Mehrabian 2016 excluded women with abnormal kidney or liver function.

Interventions

Comparisons

Three studies investigated statin monotherapy versus placebo (Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009), Banaszewska 2011 evaluated statin combined with metformin versus metformin alone, Duleba 2006 evaluated statin combined with OCP versus OCP alone, and two studies investigated statin monotherapy versus metformin (Banaszewska 2011; Mehrabian 2016). Mehrabian 2016 also evaluated statin monotherapy versus OCP plus flutamide.

Monotherapy

Puurunen 2013 and Sathyapalan 2009 compared atorvastatin (20 mg per day, orally) versus placebo, and Raja-Khan 2011 compared atorvastatin (60 mg per day, orally) versus placebo. Mehrabian 2016 compared simvastatin (20 mg per day, orally) versus metformin (500 mg three times per day, orally), and Banaszewska 2011 compared simvastatin (20 mg per day, orally) versus metformin (850 mg twice per day, orally).

Combination therapy

Two studies evaluated statin combination therapy: Banaszewska 2011 evaluated simvastatin (20 mg per day, orally) plus metformin (850 mg twice per day, orally) versus metformin (850 mg twice per day). Duleba 2006 evaluated simvastatin (20 mg/day, orally) plus OCP (ethinyl oestradiol 20 µg and desogestrel 150 µg, orally) versus the same OCP alone.

Mehrabian 2016 evaluated simvastatin versus OCP (levonorgestrel 0.15 mg and ethinyl oestradiol 0.03 mg, daily) plus flutamide (62.5 mg daily).

Follow-up

Three studies measured outcomes after approximately three months of treatment (Duleba 2006; Puurunen 2013; Sathyapalan 2009), and three studies measured outcomes after six months of treatment (Banaszewska 2011; Mehrabian 2016; Puurunen 2013). Treatment duration was six weeks in Raja-Khan 2011.

Outcomes

All studies reported biochemical or physiological measures as their primary outcomes. With respect to the primary outcomes of this review, two studies reported resumption of menstrual regularity, though they had not prespecified this outcome in any study publication (Banaszewska 2011; Sathyapalan 2009); and no studies reported spontaneous ovulation.

Serum testosterone level was the stated primary outcome of three studies (Banaszewska 2011; Duleba 2006; Puurunen 2013). Primary outcomes in the other studies were insulin sensitivity (Puurunen 2013), percentage change in brachial artery diameter after release of transient occlusion (Raja-Khan 2011), and serum hs-CRP (Sathyapalan 2009).

Secondary outcomes included lipid profile and serum insulin levels (all studies), serum testosterone (Raja-Khan 2011; Sathyapalan 2009), change in HOMA-IR (Mehrabian 2016; Sathyapalan 2009), hirsutism score (Raja-Khan 2011), and hs-CRP (Puurunen 2013).

Most studies also reported outcomes that were not prespecified. Banaszewska 2011, Duleba 2006 and Sathyapalan 2009 reported menstrual regularity. Banaszewska 2011 and Duleba 2006 also reported serum levels of hs-CRP, insulin, and advanced glycated end-products; and endothelial function. In addition, Banaszewska 2011 reported acne and hirsutism, and Duleba 2006 reported hirsutism. Sathyapalan 2009 reported serum 25-hydroxyvitamin D levels.

No studies mentioned the accuracy of analytical methods used to detect very low levels of serum testosterone and hs-CRP. However, the corresponding author of Sathyapalan 2009 informed us that the functional sensitivity for the testosterone assay was 0.14 ng/mL (95% CI 0.11 to 0.17), and the analytical sensitivity was 0.08 ng/mL for the instrument ARCHITECT. This study fulfilled the criteria with no significant effects of other interferences such as cross-reaction with aldosterone or other steroidal hormones.

No studies described any postintervention follow-up.

See the Characteristics of included studies table, Table 2, and Table 3 for baseline characteristics of participants.

Excluded studies

In the previous version of this review, we excluded four studies (Economou 2011; Kaya 2009; Kaya 2010; Kazerooni 2010).

In the current update, we excluded 14 studies after assessing full-text articles. Two were RCTs examining the effect of statins in women with PCOS actively trying to conceive (Pourmatroud 2014; Rashidi 2011), four were non-randomised (Akbari 2016; Celik 2012; Malik 2018; Yang 2016), one was a review article (Banaszewska 2010), one had the wrong study design (Navali 2011), two were systematic reviews (Gao 2012; Sun 2015), and four were studies examining the role of interventions other than statins in women with PCOS (Ghazeeri 2015; IRCT20140525017827N8; Krysiak 2015; NCT02766803). For details of each of these studies, please see the Characteristics of excluded studies table.

Studies awaiting classification

We listed eight studies as awaiting classification. Three were registered but not published. For one study, we were unable to retrieve the full text or find more information. For two, the published data were incomplete and the study authors did not respond to our request for more information. For the last two, we have contacted the study authors for confirmation of data. See the Studies awaiting classification table for details.

Risk of bias in included studies

See Figure 2 (risk of bias graph) and Figure 3 (risk of bias summary).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

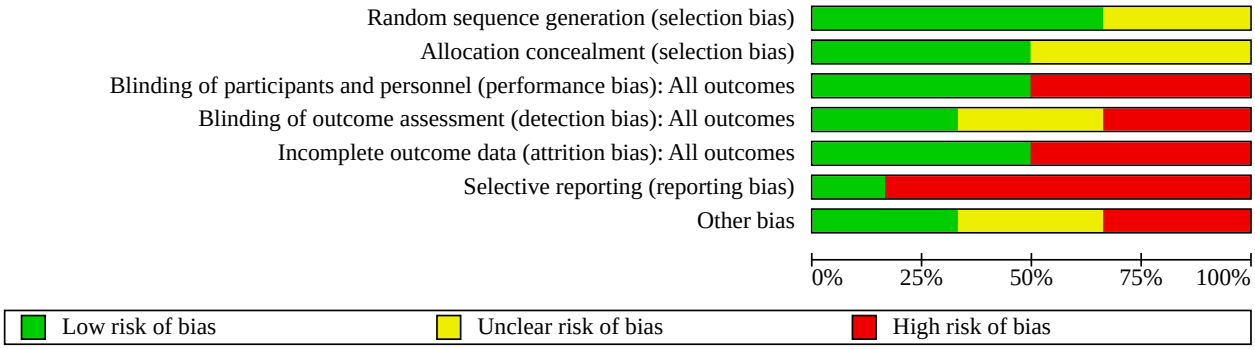
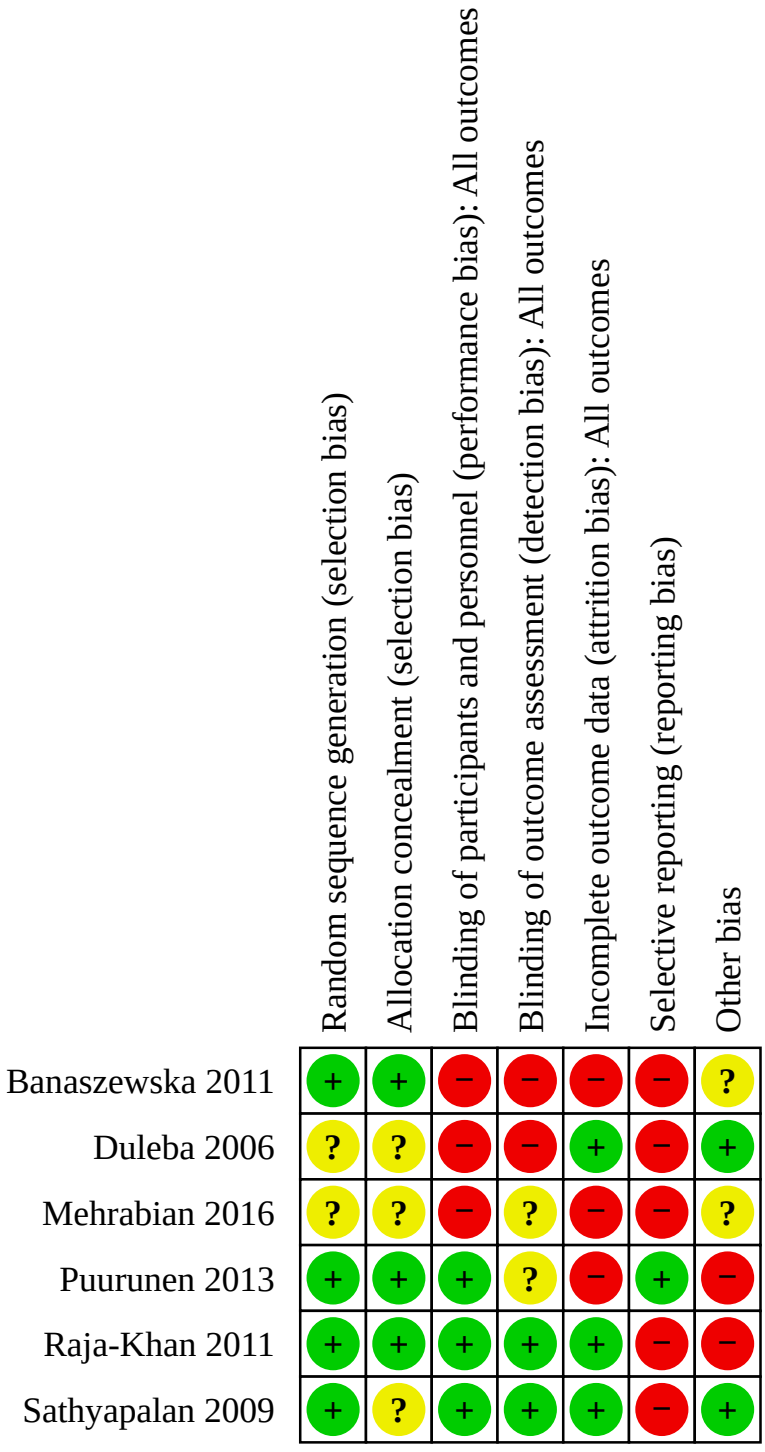


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Four studies were at low risk of selection bias related to sequence generation because they used computerised methods or a random numbers table (Banaszewska 2011; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009). Duleba 2006 and Mehrabian 2016 did not clearly describe the method of generating random sequences (unclear risk of bias).

Allocation concealment

Three studies were at low risk of selection bias related to allocation concealment (Banaszewska 2011; Puurunen 2013; Raja-Khan 2011), and three studies were at unclear risk because they did not clearly describe the methods for concealing allocation (Duleba 2006; Mehrabian 2016; Sathyapalan 2009).

Blinding

Three studies were at high risk of performance bias (Banaszewska 2011; Duleba 2006; Mehrabian 2016), and three were at low risk (Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009). Raja-Khan 2011 and Sathyapalan 2009 were at low risk of detection bias because they were described as double-blind, whereas Banaszewska 2011 and Duleba 2006 were at high risk because they were open-label studies. The remaining two studies were at unclear risk of detection bias: Mehrabian 2016 was a single-blind study, and the method of blinding was unclear in Puurunen 2013. No study publication described checking of blinding conditions or any precautions taken when blinding lipid profile data in the follow-up and endpoint evaluation. The corresponding author of Sathyapalan 2009 informed us that the investigators maintained blinding at the two measurement time points (baseline and endpoint).

Incomplete outcome data

Risk of attrition bias was low in three studies, which had no or few dropouts (Duleba 2006; Sathyapalan 2009) or used ITT analysis (Raja-Khan 2011). The risk of attrition bias was high in three studies, which had attrition rates of 8.1% (Mehrabian 2016), 16.9% (Banaszewska 2011), and 29% (Puurunen 2013), and used per-protocol analysis. For details on attrition rates in each study, see Table 3.

Selective reporting

There was a high risk of reporting bias in five studies (Banaszewska 2011; Duleba 2006; Mehrabian 2016; Raja-Khan 2011; Sathyapalan 2009). Three studies reported clinical outcomes that were not prespecified in the methods section of the full-text articles (Banaszewska 2011; Duleba 2006; Sathyapalan 2009). Mehrabian 2016 did not report some outcomes prespecified in the study register (e.g. there were no reported follow-up data on insulin resistance). Puurunen 2013 was at low risk of selective reporting because all outcomes mentioned in the methods section were reported in the results, and there were no additional outcomes.

Other potential sources of bias

Raja-Khan 2011 was at high risk of other bias due to a significant difference in baseline BMI between the two groups. Puurunen 2013 also had significant differences in the baseline characteristics of glucose, insulin, and testosterone and was assessed as high risk. Banaszewska 2011 reported significant baseline differences between the groups in HDL and follicle stimulating hormone, and Mehrabian 2016 reported differences in waist circumference, while BMI was comparable. The potential for bias was unclear in these two studies. Duleba 2006 and Sathyapalan 2009 appeared to be at low risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Statin compared to placebo for women with polycystic ovary syndrome not actively trying to conceive; **Summary of findings 2** Statin plus metformin compared to metformin alone for women with polycystic ovary syndrome not actively trying to conceive; **Summary of findings 3** Statin plus oral contraceptive pill compared to oral contraceptive pill alone for women with polycystic ovary syndrome not actively trying to conceive; **Summary of findings 4** Statin compared to metformin for women with polycystic ovary syndrome not actively trying to conceive; **Summary of findings 5** Statin compared to oral contraceptive pill plus flutamide for women with polycystic ovary syndrome not actively trying to conceive

1. Statin versus placebo

Three studies evaluated statins versus placebo (Puurunen 2013, Raja-Khan 2011, Sathyapalan 2009). They compared the effects of statins and metformin after six weeks (Raja-Khan 2011), three months (Sathyapalan 2009), and six months of treatment (Puurunen 2013). See Summary of findings 1.

Primary outcomes

1.1 Resumption of menstrual regularity

Only Sathyapalan 2009 reported resumption of menstrual regularity (as length of menstrual cycle in days). We are uncertain if statins compared with placebo shorten mean length of menstrual cycle (MD −2.00 days, 95% CI −24.86 to 20.86; 37 participants; very low-certainty evidence; Analysis 1.1).

1.2 Resumption of spontaneous ovulation

No studies reported resumption of spontaneous ovulation.

Secondary outcomes

1.3 Improvement in body composition

1.3.1 Body mass index

All three studies provided analysable data on BMI. We are uncertain if statins reduce BMI compared with placebo (MD 1.06 kg/m^2, 95% CI −1.87 to 3.99; I^2 = 3%; 3 RCTs, 85 participants; very low-certainty evidence; Analysis 1.2). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.3.2 Waist circumference

Only Sathyapalan 2009 reported waist circumference. We are uncertain of the effect of statins on waist circumference compared with placebo (MD 0.20 cm, 95% CI −5.76 to 6.16; 37 participants; very low-certainty evidence; Analysis 1.3). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.3.3 Waist-hip ratio

Only Puurunen 2013 reported WHR. We are uncertain of the effect of statins on WHR compared with placebo (MD 0.03, 95% CI −0.02

to 0.08; 28 participants; very low-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.4 Improvement in hirsutism

No studies reported hirsutism.

1.5 Improvement in acne severity

No studies reported acne severity.

1.6 Improvement in testosterone level

All three studies reported testosterone level. We are uncertain if statins compared with placebo reduce testosterone levels after six weeks (MD 0.06 nmol/L, 95% CI −0.72 to 0.84; 1 RCT, 20 participants; very low-certainty evidence; Analysis 1.5), 3 months (MD −0.53 nmol/L, 95% CI −1.61 to 0.54; 2 RCTs, 64 participants; very low-certainty evidence; Analysis 1.5), or six months (MD 0.10 nmol/L, 95% CI −0.43 to 0.63; 1 RCT, 28 participants; very low-certainty evidence; Analysis 1.5).

1.7 Improvement in lipid profile

1.7.1 Total cholesterol

All three studies reported total cholesterol. Compared with placebo, statins may reduce total cholesterol (MD −1.31 mmol/L, 95% CI −1.64 to −0.97; I^2 = 0%; 3 RCTs, 85 participants; low-certainty evidence; Analysis 1.6). We downgraded the certainty of the evidence once each for imprecision and risk of bias.

1.7.2 Low-density lipoprotein cholesterol

All three studies reported LDL cholesterol. Compared with placebo, statins may reduce LDL cholesterol (MD −1.10 mmol/L, 95% CI −1.38 to −0.81; I^2 = 0%; 3 RCTs, 85 participants; low-certainty evidence; Analysis 1.7). We downgraded the certainty of the evidence once each for imprecision and risk of bias.

1.7.3 High-density lipoprotein cholesterol

All three studies reported HDL cholesterol. Compared with placebo, statins may have little or no effect on HDL cholesterol (MD 0.00 mmol/L, 95% CI −0.15 to 0.15; I^2 = 0%; 3 RCTs, 85 participants; low-certainty evidence; Analysis 1.8). We downgraded the certainty of the evidence once each for imprecision and risk of bias.

1.7.4 Triglycerides

All three studies reported triglycerides. Statins may lower triglyceride levels compared with placebo (MD −0.39 mmol/L, 95% CI −0.60 to −0.18; I^2 = 37%; 3 RCTs, 85 participants; low-certainty evidence; Analysis 1.9). We downgraded the certainty of the evidence once each for imprecision and risk of bias.

1.8 Improvement in high-sensitivity C-reactive protein

All the three studies provided analysable data on hs-CRP. Compared with placebo, we are uncertain if statins reduce hs-CRP levels (MD −7.76 nmol/L, 95% CI −20.99 to 5.48; I^2 = 0%; 3 RCTs, 84 participants; very low-certainty evidence; Analysis 1.10). We downgraded the certainty of the evidence once each for imprecision and risk of bias.

1.9 Improvement in insulin sensitivity

1.9.1 Fasting insulin

All three studies provided analysable data for fasting insulin. We are uncertain if statins improve fasting insulin levels compared with placebo (MD −0.31 µIU/mL, 95% CI −5.18 to 4.57) I^2 = 55%; 3 RCTs, 85 participants; very low-certainty evidence; Analysis 1.11). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.9.2 Glucose/insulin ratio

No studies reported glucose/insulin ratio.

1.9.3 Homeostatic model assessment for insulin resistance

Only Sathyapalan 2009 reported HOMA-IR. We are uncertain if statins reduce HOMA-IR compared with placebo (MD −1.10, 95% CI −2.35 to 0.15; 37 participants; very low-certainty evidence; Analysis 1.12). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.9.4 Standard measures from euglycaemic clamps or intravenous glucose tolerance tests

Puurunen 2013 reported intravenous glucose tolerance test (IVGTT) insulin sensitivity. Statins may reduce insulin sensitivity measured by IVGTT compared with placebo (MD −3.50, 95% CI −6.06 to −0.94; 28 participants; low-certainty evidence; Analysis 1.13). We downgraded the certainty of the evidence twice for imprecision and once for risk of bias.

1.10 Adverse effects

In Puurunen 2013, one woman in the statin group stopped treatment because of arthralgia and one woman in the placebo group withdrew because of myalgia. Sathyapalan 2009 stated that no adverse events occurred in either the placebo or the atorvastatin group. Raja-Khan 2011 did not report adverse events.

2. Statin plus metformin versus metformin

One study evaluated statin plus metformin versus metformin and compared the effects of statins and metformin after six months (Banaszewska 2011). See Summary of findings 2.

Primary outcomes

2.1 Resumption of menstrual regularity

Banaszewska 2011 reported resumption of menstrual regularity as number of spontaneous menses per six months. We are uncertain if statins plus metformin improves resumption of menstrual regularity compared with metformin alone (MD 0.60 menses, 95% CI 0.08 to 1.12; 69 participants; very low-certainty evidence; Analysis 2.1).

2.2 Resumption of spontaneous ovulation

Banaszewska 2011 did not report resumption of spontaneous ovulation.

Secondary outcomes

2.3 Improvement in body composition

2.3.1 Body mass index

We are uncertain if statins plus metformin reduces BMI compared with metformin alone (MD −0.42 kg/m^2, 95% CI −1.25 to 0.41;

69 participants; very low-certainty evidence; Analysis 2.2). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.3.2 Waist circumference

Banaszewska 2011 did not report waist circumference.

2.3.3 Waist-hip ratio

Banaszewska 2011 did not report WHR.

2.4 Improvement in hirsutism

We are uncertain if statins plus metformin compared with metformin alone improves hirsutism measured using the Ferriman-Gallwey score (MD −0.16, 95% CI −0.91 to 0.59; 69 participants; very low-certainty evidence; Analysis 2.3).

2.5 Improvement in acne severity

Banaszewska 2011 reported acne severity using a four-point clinical scale (0 = no acne; 1 = minor acne on the face only; 2 = moderate acne on the face only; 3 = severe acne on the face and back or chest). We are uncertain if statins plus metformin compared with metformin alone improves acne severity (MD −0.31, 95% CI −0.67 to 0.05; 69 participants; very low-certainty evidence; Analysis 2.4).

2.6 Improvement in testosterone level

We are uncertain if statins plus metformin improves serum testosterone compared with metformin alone (MD −0.03 nmol/L, 95% CI −0.37 to 0.31; 69 participants; very low-certainty evidence; Analysis 2.5).

2.7 Improvement in lipid profile

2.7.1 Total cholesterol

It is unclear if statins plus metformin reduces total cholesterol compared with metformin alone, because the evidence is of very low certainty (MD −0.97 mmol/L, 95% CI −1.34 to −0.60; 69 participants; very low-certainty evidence; Analysis 2.6). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.7.2 Low-density lipoprotein cholesterol

It is unclear if statins plus metformin compared with metformin alone reduces LDL cholesterol, because the evidence is of very low certainty (MD −0.89 mmol/L, 95% CI −1.20 to −0.58, very low-certainty evidence; Analysis 2.7). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.7.3 High-density lipoprotein cholesterol (mmol/L)

It is unclear if statins plus metformin improves HDL levels compared with metformin alone (MD −0.03 mmol/L, 95% CI −0.17 to 0.11; 69 participants; very low-certainty evidence; Analysis 2.8). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.7.4 Triglycerides (mmol/L)

It is unclear if statins plus metformin compared with metformin alone reduce triglycerides, because the evidence is of very low certainty (MD −0.29 mmol/L, 95% CI −0.51 to −0.07; 69 participants; very low-certainty evidence; Analysis 2.9). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.8 Improvement in high-sensitivity C-reactive protein

Banaszewska 2011 did not report hs-CRP.

2.9 Improvement in insulin sensitivity

2.9.1 Fasting insulin

It is unclear if statins plus metformin compared with metformin alone decreases fasting insulin levels, because the evidence is of very low certainty (MD −2.45 µIU/mL, 95% CI −4.91 to 0.01; 69 participants; very low-certainty evidence; Analysis 2.10). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

2.9.2 Glucose/insulin ratio

Banaszewska 2011 did not report glutose/insulin ratio.

2.9.3 Homeostatic model assessment for insulin resistance

Banaszewska 2011 did not report HOMA-IR.

2.9.4 Standard measures from euglycaemic clamps or intravenous glucose tolerance tests

Banaszewska 2011 did not report any standard measures from euglycaemic clamps or intravenous glucose tolerance tests.

2.10 Adverse effects

Banaszewska 2011 reported that no significant adverse events occurred.

3. Statin plus oral contraceptive pill versus oral contraceptive pill alone

One study evaluated statin plus OCP versus OCP alone (Duleba 2006). The reported treatment duration was 12 weeks. See Summary of findings 3.

Primary outcomes

3.1 Resumption of menstrual regularity

Duleba 2006 did not report resumption of menstrual regularity.

3.2 Resumption of spontaneous ovulation

Duleba 2006 did not report resumption of spontaneous ovulation.

Secondary outcomes

3.3 Improvement in body composition

3.3.1 Body mass index

It is unclear if statins plus OCP compared with OCP alone improves BMI (MD 0.05 kg/m^2, 95% CI −0.41 to 0.51; 48 participants; very low-certainty evidence; Analysis 3.1). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.3.2 Waist circumference

Duleba 2006 did not report waist circumference.

3.3.3 Waist-hip ratio

Duleba 2006 did not report WHR.

3.4 Improvement in hirsutism

We are uncertain if statins plus OCP compared with OCP alone improves hirsutism measured using the Ferriman-Gallwey score (MD −0.12, 95% CI −0.41 to 0.17; 48 participants; very low-certainty evidence; Analysis 3.2).

3.5 Improvement in acne severity

Duleba 2006 did not report acne severity.

3.6 Improvement in testosterone level

It is unclear if statins plus OCP compared with OCP alone reduces testosterone levels, because the certainty of the evidence is very low (MD −0.82 nmol/L, 95% CI −1.38 to −0.26; 48 participants; very low-certainty evidence; Analysis 3.3).

3.7 Improvement in lipid profile

3.7.1 Total cholesterol

It is unclear if statins plus OCP compared with OCP alone decreases total cholesterol levels, because the certainty of the evidence is very low (MD −0.93 mmol/L, 95% CI −1.33 to −0.53; 48 participants; very low-certainty evidence; Analysis 3.4). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.7.2 Low-density lipoprotein cholesterol

It is unclear if statins plus OCP compared with OCP alone decreases LDL cholesterol, because the certainty of the evidence is very low (MD −0.74 mmol/L, 95% CI −1.14 to −0.34; 48 participants; very low-certainty evidence; Analysis 3.5). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.7.3 High-density lipoprotein cholesterol

We are uncertain if statins plus OCP compared with OCP alone increases HDL cholesterol (MD −0.06 mmol/L, 95% CI −0.22 to 0.10; 48 participants; very low-certainty evidence; Analysis 3.6). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.7.4 Triglycerides

We are uncertain if statins plus OCP compared with OCP alone decreases triglycerides, because the certainty of the evidence is very low (MD −0.18 mmol/L, 95% CI −0.41 to 0.05; 48 participants; very low-certainty evidence; Analysis 3.7). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.8 Improvement in high-sensitivity C-reactive protein

Duleba 2006 did not report hs-CRP.

3.9 Improvement in insulin sensitivity

3.9.1 Fasting insulin

We are uncertain if statins plus OCP compared with OCP alone improves fasting insulin (MD 0.60 µIU/mL, 95% CI −2.15 to 3.35; 48 participants; very low-certainty evidence; Analysis 3.8). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.9.2 Glucose/insulin ratio

Duleba 2006 did not report glucose/insulin ratio.

3.9.3 Homeostatic model assessment for insulin resistance

We are uncertain if statins plus OCP compared with OCP alone reduces HOMA-IR (MD −1.16, 95% CI −3.19 to 0.87; 48 participants; very low-certainty evidence; Analysis 3.9). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

3.9.4 Standard measures from euglycaemic clamps or intravenous glucose tolerance tests

Duleba 2006 did not report any standard measures from euglycaemic clamps or intravenous glucose tolerance tests.

3.10 Adverse effects

Duleba 2006 reported that no women experienced significant side effects, and all women completed the 12-week treatment course.

4. Statin versus metformin

Two studies compared the effects of statins with the effects of metformin after six months of treatment (Banaszewska 2011; Mehrabian 2016). See Summary of findings 4.

Primary outcomes

4.1 Resumption of menstrual regularity

Only Banaszewska 2011 reported resumption of menstrual regularity (as number of spontaneous menses per six months). We are uncertain if statins improve menstrual regularity compared with metformin (MD 0.50 menses, 95% CI −0.05 to 1.05; 61 participants; very low-certainty evidence; Analysis 4.1).

4.2 Resumption of spontaneous ovulation

No studies reported resumption of spontaneous ovulation.

Secondary outcomes

4.3 Improvement in body composition

4.3.1 Body mass index

We are uncertain if statins improve BMI compared with metformin (MD −0.14 kg/m^2, 95% CI −1.53 to 1.25; I^2 = 98%; 2 RCTs, 129 participants; very low-certainty evidence; Analysis 4.2). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

4.3.2 Waist circumference

Only Mehrabian 2016 reported wait circumference. It is unclear if statins compared with metformin decrease waist circumference, because the certainty of the evidence is very low (MD −1.64 cm, 95% CI −2.24 to −1.04; 68 participants; very low-certainty evidence; Analysis 4.3). We downgraded the certainty of the evidence one level each for risk of bias concerns, imprecision, and indirectness.

4.3.3 Waist-hip-ratio

No studies reported WHR.

4.4 Improvement in hirsutism

Only Banaszewska 2011 reported hirsutism. We are uncertain if statins compared with metformin reduce hirsutism measured using the Ferriman-Gallwey score (MD −0.26, 95% CI −0.97 to 0.45; 61 participants; very low-certainty evidence; Analysis 4.4).

4.5 Improvement in acne severity

Only Banaszewska 2011 reported acne severity, using a four-point clinical scale (0 = no acne; 1 = minor acne on the face only; 2 = moderate acne on the face only; 3 = severe acne on the face and back or chest). We are uncertain if statins reduce acne compared with metformin (MD −0.18, 95% CI −0.53 to 0.17; 61 participants; very low-certainty evidence; Analysis 4.5).

4.6 Improvement in testosterone level

Only Banaszewska 2011 reported testosterone levels. We are uncertain if statins decrease serum testosterone compared with metformin (MD −0.24 nmol/L, 95% CI −0.58 to 0.10; 61 participants; very low-certainty evidence; Analysis 4.6).

4.7 Improvement in lipid profile

4.7.1 Total cholesterol

Only Banaszewska 2011 reported total cholesterol. Compared with metformin, statins may reduce total cholesterol (MD −0.99 mmol/L, 95% CI −1.38 to −0.60; 1 RCT, 61 participants; low-certainty evidence; Analysis 4.7). We downgraded the certainty of the evidence one level each for imprecision and risk of bias.

4.7.2 Low-density lipoprotein cholesterol

Only Banaszewska 2011 reported LDL cholesterol. Compared with metformin, statins may reduce LDL cholesterol (MD −0.91 mmol/L, 95% CI −1.24 to −0.58; 1 RCT, 61 participants; low-certainty evidence; Analysis 4.8). We downgraded the certainty of the evidence one level each for imprecision and risk of bias.

4.7.3 High-density lipoprotein cholesterol

Both studies reported HDL cholesterol. Compared with metformin, statins may have little or no effect on HDL cholesterol (MD 0.00 mmol/L, 95% CI −0.02 to 0.02; I^2 = 0%; 2 RCTs, 129 participants; low-certainty evidence; Analysis 4.9). We downgraded the certainty of the evidence one level each for imprecision and risk of bias.

4.7.4 Triglycerides

Both studies reported triglycerides. Compared with metformin, statins may reduce triglycerides (MD −0.19 mmol/L, 95% CI −0.29 to −0.10; I^2 = 0%; 2 RCTs, 129 participants; low-certainty evidence; Analysis 4.10). We downgraded the certainty of the evidence one level each for imprecision and risk of bias.

4.8 Improvement in high-sensitivity C-reactive protein

Only Mehrabian 2016 reported hs-CRP. It is unclear if statins compared with metformin reduce hs-CRP, because the certainty of the evidence is very low (MD −1.62 nmol/L, 95% CI −2.60 to −0.64; 68 participants; very low-certainty evidence; Analysis 4.11). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

4.9 Improvement in insulin sensitivity

4.9.1 Fasting insulin

Only Banaszewska 2011 reported fasting insulin. We are uncertain if statins compared with metformin have an effect on fasting insulin levels (MD −1.01 µIU/mL, 95% CI −3.27 to 1.25; 61 participants; very low-certainty evidence; Analysis 4.12). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

4.9.2 Glucose/insulin ratio

No studies reported glucose/insulin ratio.

4.9.3 Homeostatic model assessment for insulin resistance

No studies reported HOMA-IR.

4.9.4 Standard measures from euglycaemic clamps or intravenous glucose tolerance tests

No studies reported any standard measures from euglycaemic clamps or intravenous glucose tolerance tests.

4.10 Adverse effects

Banaszewska 2011 reported that six women using metformin experienced transient gastrointestinal side effects including diarrhoea; however, these women did not discontinue treatment. Mehrabian 2016 reported that no participants experienced significant side effects.

5. Statin versus oral contraceptive pill plus flutamide

Mehrabian 2016 compared the effects of statin versus the effects of OCP in combination with flutamide. See Summary of findings 5.

Primary outcomes

5.1 Resumption of menstrual regularity

Mehrabian 2016 did not report resumption of menstrual regularity.

5.2 Resumption of spontaneous ovulation

Mehrabian 2016 did not report resumption of spontaneous ovulation.

Secondary outcomes

5.3 Improvement in body composition

5.3.1 Body mass index

We are uncertain if statins compared with OCP plus flutamide improve BMI, because the certainty of the evidence is very low (MD −1.05 kg/m^2, 95% CI −1.23 to −0.87; 68 participants; very low-certainty evidence; Analysis 5.1). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

5.3.2 Waist circumference

It is unclear if statins improve waist circumference compared with OCP plus flutamide, because the certainty of the evidence is very low (MD −1.91 cm, 95% CI −2.49 to −1.33; 68 participants; very low-certainty evidence; Analysis 5.2). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

5.3.3 Waist-hip-ratio

Mehrabian 2016 did not report WHR.

5.4 Improvement in hirsutism

Mehrabian 2016 did not report hirsutism.

5.5 Improvement in acne severity

Mehrabian 2016 did not report acne severity.

5.6 Improvement in testosterone levels

Mehrabian 2016 did not report testosterone levels.

5.7 Improvement in lipid profile

5.7.1 Total cholesterol

Mehrabian 2016 did not report total cholesterol.

5.7.2 Low-density lipoprotein cholesterol

Mehrabian 2016 did not report LDL cholesterol.

5.7.3 High-density lipoprotein cholesterol

We are uncertain if statins improve HDL levels compared with OCP plus flutamide (MD 0.00 mmol/L, 95% CI −0.02 to 0.02; 68 participants; very low-certainty evidence; Analysis 5.3). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

5.7.4 Triglycerides

It is unclear if statins compared with OCP plus flutamide improve triglyceride levels, because the certainty of the evidence is very low (MD −0.14 mmol/L, 95% CI −0.24 to −0.04; 68 participants; very low-certainty evidence; Analysis 5.4). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

5.8 Improvement in high-sensitivity C-reactive protein

We are uncertain if statins reduce hs-CRP compared with OCP plus flutamide (MD 0.48 nmol/L, 95% CI −0.93 to 1.89; 68 participants; very low-certainty evidence; Analysis 5.5). We downgraded the certainty of the evidence twice for imprecision and twice for risk of bias.

5.9 Improvement in insulin sensitivity

5.9.1 Fasting insulin

Mehrabian 2016 did not report fasting insulin.

5.9.2 Glucose/insulin ratio

Mehrabian 2016 did not report glucose/insulin ratio.

5.9.3 Homeostatic model assessment for insulin resistance

Mehrabian 2016 did not report HOMA-IR.

5.9.4 Standard measures from euglycaemic clamps or intravenous glucose tolerance tests

Mehrabian 2016 did not report any standard measures from euglycaemic clamps or intravenous glucose tolerance tests.

5.10 Adverse effects

Mehrabian 2016 reported that no women experienced any significant side effects.

Sensitivity analysis

We were unable to perform any of the prespecified sensitivity analyses due to insufficient data.

Assessment of publication bias

We could not assess publication bias due to insufficient data.

DISCUSSION

Summary of main results

This review aimed to generate evidence on the efficacy and safety of statins for the treatment of hyperandrogenism and adverse metabolic parameters of PCOS in women who were not actively attempting to conceive. We included six studies that evaluated the effect of statins (alone or in combination with OCP or metformin) on different clinical outcomes. The main reported outcomes were resumption of menstrual regularity, improvement in hirsutism, and improvement in acne severity. The certainty of the evidence was very low for all our main outcomes with analysable data. No studies reported resumption of spontaneous ovulation. In terms of biochemical parameters, the studies evaluating statins versus placebo or statins plus metformin versus metformin showed no significant reduction in serum testosterone concentration (a surrogate indicator of hirsutism or acne in most studies). Duleba 2006 found that statins plus OCP compared with OCP alone decreased testosterone levels but did not improve hirsutism; however, the certainty of the evidence was very low, so the results should be interpreted with caution. As expected, we found that statins compared with placebo may reduce total cholesterol, LDL cholesterol, and triglyceride levels, which are the surrogate markers for cardiovascular outcomes. However, we found no evidence of effect for statins (alone or in combination with OCP or metformin) on serum HDL concentration. We also found no evidence of an effect of statin use (alone or combination with OCP or metformin) on serum fasting insulin concentration, hs-CRP, or HOMA-IR. This suggests that statins may have limited efficacy for treating hyperinsulinaemia or metabolic syndrome in women with PCOS. There was very limited evidence on the effect of statins on body composition; we found very low-certainty evidence from different studies of no effect on waist circumference and BMI.

Two studies examined the efficacy and safety of statins versus metformin (Banaszewska 2011; Mehrabian 2016). Compared with metformin, statin monotherapy may reduce total cholesterol, LDL cholesterol, triglycerides, and hs-CRP. There was no evidence of a difference in the effect of statins compared with metformin on testosterone levels, acne severity, hirsutism, or HDL cholesterol. Banaszewska 2011 found that statins had a slight beneficial effect on resumption of menstrual regularity, and Mehrabian 2016 found that statin monotherapy improved waist circumference, but the certainty of the evidence was very low for both outcomes. Most results from these two studies were consistent, though not for BMI. Both studies used the same statin (simvastatin 20 mg, orally, once per day). The discordant BMI results may be due to different dosages of metformin (850 mg twice per day in Banaszewska 2011 and 1000 mg once per day in Mehrabian 2016). A higher dose of metformin may help to lower BMI.

The studies that recorded adverse effects reported either that no significant adverse effects occurred, or that there were no differences between the intervention and control groups. All studies had a short duration (six weeks to six months); long-term data on the comparative effects of statins are lacking.

Overall completeness and applicability of evidence

Overall, all studies clearly defined their populations and the diagnostic criteria of PCOS, but the diagnostic criteria differed across studies. In addition, there were significant baseline

differences between study groups; for example, in Puurunen 2013, the women treated with statins had higher fasting insulin, testosterone, and free androgen index.

Owing to the limited number of eligible studies, we were unable to perform sensitivity analyses to check the effect of the differences in diagnostic criteria. Furthermore, there were differences in BMI and serum insulin levels between the included studies at baseline. In Duleba 2006, the participants had a normal BMI, and more than 50% of women in the OCP group had a serum testosterone level below 80 ng/dL and an insulin level below 15 µIU/L, whereas Sathyapalan 2009 and Raja-Khan 2011 included obese women with high insulin levels. Data in this review are derived from women with PCOS who were recruited from sites in Europe, the USA, and Iran. This may limit the applicability of our results, if ethnic variation affects the risk of clinical or metabolic adverse outcomes or responses to statin therapy.

There are a limited number of RCTs evaluating statins versus placebo or statins combined with another drug versus the other drug alone. Another factor that may limit the applicability of this review is the small sample sizes, which translated to imprecise results and low confidence in the conclusions. We were unable to perform some planned analyses owing to the limited number of studies.

The included studies only partially addressed the objectives of this review in terms of reporting of outcomes. Only two studies reported our primary outcome resumption of menstrual regularity, and no studies reported resumption of ovulation, which was our second primary outcome.

Three studies measured serum testosterone as a primary outcome. Because the evidence was of very low certainty, we could not confirm if statins were effective in reducing testosterone levels. There are insufficient studies to date assessing whether a favourable biochemical androgen profile leads to improvement in the symptoms of hirsutism and acne. In addition, the number of readings and timing for serum testosterone measurement affect the internal validity of the study result, so primary studies should describe measurement methods in detail. Some studies in this review took only a single reading at baseline and the endpoint. There were no serious adverse events reported, but the studies provided no data to confirm the safety profile of statins in women with PCOS in the long term. While statins were previously considered teratogenic, more recent evidence has refuted these concerns surrounding statins in pregnancy (Karalis 2016; Ma'ayeh 2020).

No studies mentioned the time of administration of statins, though this factor influences their efficacy: there are sufficient data to support evening administration of simvastatin, as a short-acting statin, for achieving optimal lowering of LDL cholesterol (Awad 2018).

Quality of the evidence

For details see Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4, and Summary of findings 5. The certainty of the evidence for all main outcomes was very low.

All studies were at high risk of bias in at least one domain. Duleba 2006 and Mehrabian 2016 did not clearly describe the methods used for random sequence generation or allocation concealment. Banaszewska 2011 and Duleba 2006 were at high risk of performance and detection bias, and all studies except Puurunen 2013 were at high risk of reporting bias. We downgraded the certainty of the evidence for all outcomes for serious or very serious risk of bias concerns.

Another reason for downgrading the certainty of the evidence was serious or very serious imprecision. All results were constrained by small numbers of participants, which led to wide CIs (indicating limited precision). Meta-analysis was not possible for most primary and secondary outcomes because no trials or only a single trial provided analysable data. There is a need for well-designed RCTs with large sample sizes to confirm or refute the current evidence.

Potential biases in the review process

To limit bias in the review process, the CGF Group guided and developed the search, applying no restrictions on language of publication. Two review authors independently performed study selection, risk of bias assessment, and data collection, resolving any disagreements by discussion with a third review author. When contact details were available, we contacted authors of potentially eligible trials for more information. We have listed some studies as awaiting classification pending confirmation of study data by study authors.

Agreements and disagreements with other studies or reviews

Since the publication of the previous version of this review in 2011 (Raval 2011), five systematic reviews have examined the effect of statins on clinical and biochemical parameters in women with PCOS (Abdalla 2022; Chen 2021a; Chen 2021b; Liu 2021; Miao 2022).

Abdalla 2022 included three studies, one of which was excluded from our review (not truly randomised), to analyse the effect of atorvastatin on lipid profiles and CRP in PCOS. Abdalla 2022 and our review reached similar conclusions regarding the effect of statins on lipid profiles and CRP.

Chen 2021a focussed on the effect of statins on hyperandrogenism in women with PCOS; it included nine studies, five of which were also included in our review. The remaining four studies were either excluded from our review (not truly randomised) or listed as awaiting classification due to data integrity concerns. As a result, there are some inconsistencies between our results and those of Chen 2021a.

Chen 2021b included nine studies and analysed the effects of atorvastatin on insulin resistance in women with PCOS. The women in the atorvastatin group had lower fasting insulin levels than those in the placebo group, whereas we found no significant differences between the statin and placebo groups. However, Chen 2021b reported decreased HOMA-IR with atorvastatin therapy, as in our review.

Liu 2021 studied the efficacy and safety of metformin combined with simvastatin for the treatment of PCOS. It included two RCTs published by the same author group (one of which was Banaszewska 2011). Liu 2021 included results from different durations (three months and six months) of the same clinical trial, so there is a possibility of duplicate data. We included data reported after six months of treatment only.

Miao 2022 included 13 studies to analyse the effect of statins (alone or in combination with metformin) on PCOS, and did not group publications from the same trials. The results showed a significant decline in total testosterone with statins, whereas our meta-analyses produced uncertain results for this outcome. Miao 2022 also demonstrated a significant improvement in lipid profile, glucose metabolism, and hs-CRP, which was consistent with our results.

There is a 2021 Cochrane Review investigating the effects of statins on testosterone levels in male and female populations, including women with PCOS (Shawish 2021); that review included three of the studies included in our review (Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009). Shawish 2021 concluded that atorvastatin compared with placebo decreased total testosterone levels in women with PCOS, whereas we found no evidence of a difference in testosterone levels between statin and placebo (very low-certainty evidence). The difference in results is due to the fact that Shawish 2021 pooled all studies regardless of duration of treatment in one analysis. When we analysed the results per subgroup based on duration of treatment, we saw no such effect of statin on testosterone levels; only one study showed a reduction (Sathyapalan 2009). In addition, the analyses in Shawish 2021 comparing the effect of statins versus placebo on testosterone levels also included data from Akbari 2016, which we excluded because it used a sequential non-random sampling method.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for all main outcomes of this review was of very low certainty. Due to the limited evidence, we are uncertain if statins compared with placebo, or statins plus metformin compared with metformin alone, improve resumption of menstrual regularity in women with polycystic ovary syndrome (PCOS) not actively trying to conceive. The study comparing statins plus oral contraceptive pill (OCP) versus OCP alone reported neither of our primary outcomes. No studies reported resumption of spontaneous ovulation. We are uncertain if statins alone improve hirsutism, acne, or testosterone levels compared with placebo, metformin, or OCP. We are also uncertain if statins plus metformin versus metformin alone or statins plus OCP versus OCP alone improve hirsutism, acne, or testosterone levels. There were no reported differences in adverse effects between treatment groups.

Implications for research

Consumer-related outcomes are of major concern in the field of gynaecology, which means studies must measure adverse events. Limited data were available on the efficacy of statins for improving resumption of menstrual regularity, hirsutism, or acne; and there were no data on resumption of spontaneous ovulation. There is a need for large studies with primary outcomes such as resumption of menstrual cycle and resumption of ovulation. It is important to report the time of administration of certain statins. Future studies should include large sample sizes and take precautions to minimise potential bias in outcome measurement.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Banaszewska 2011

Study characteristics	
Methods	**Sequence generation and allocation:** participants allocated to 3 groups in 1:1:1 allocation ratio with block sizes of 6, 9, and 12. Random number table and block size determination. **Blinding:** open-label **Study period:** December 2006–March 2009

Participants	**Inclusion criteria**
	
	• PCOS diagnosis based on the modified Rotterdam criteria: ≥ 2 of:
	  ◦ clinical or chemical hyperandrogenism;
	  ◦ oligomenorrhoea or amenorrhoea; or
	  ◦ polycystic ovaries as viewed by transvaginal ultrasound.
	• Normal baseline renal function tests, bilirubin, and aminotransferases
	
	Exclusion criteria
	
	• Congenital adrenal hyperplasia
	• Cushing syndrome
	• Androgen-secreting tumours
	• Thyroid disease
	• Hyperprolactinaemia
	• Diabetes mellitus
	• Use of any OCP, steroids, or medications that interfere with steroid hormones, ovarian functions, insulin sensitivity, or lipid metabolism within 3 months of starting trial
	
	Compliance to statins: not reported

Interventions	**Intervention(s)** • Simvastatin 20 mg orally once a day plus metformin 850 mg orally twice a day • Simvastatin 20 mg orally once a day **Comparator(s)** • Metformin 850 mg orally twice a day **Treatment duration:** 6 months (with intermediate analysis at 3 months) **Comedication:** none
Outcomes	**Primary outcome(s)** • Testosterone level (total and free) by electro-chemiluminescence assay **Secondary outcome(s)** • Number of spontaneous menses per 6 months • Ovarian volume • BMI* • Hirsutism measured on the Ferriman-Gallwey scale* • Acne measured with acne scale* • Serum LH • Serum FSH • Serum prolactin* • SHBG* • LDL cholesterol

Banaszewska 2011 *(Continued)*

- HDL cholesterol
- Total cholesterol
- Triglycerides
- sVCAM-1
- Serum DHEAS
- Fasting serum insulin
- Fasting serum glucose*
- hs-CRP*
- Insulin sensitivity index

*not prespecified in protocol

Other outcome(s): none

Notes

Country: Poland

Setting: Division of Fertility and Reproductive Endocrinology, Poznan University of Medical Sciences

Funding: Polish State Committee for Scientific Research grant and Eunice Kennedy Shriver National Institute of Child Health and Human Development grant; Study drugs were supplied by pharmaceutical companies (i.e. simvastatin from Polfa Grodzisk Mazowiecki and OCP from Organone Polska).

Trial registration:clinicaltrials.gov/ct2/show/NCT00396513

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Low risk	Quote: "At the time of randomisation, sequentially numbered, sealed envelopes were opened. Allocation to study group was concealed until a consent was obtained and inclusion/exclusion criteria verified. The randomisation list was kept locked, and the allocation numbers were generated and sealed in the envelopes by one of the authors."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 70% completed study, analysis was per protocol.
Selective reporting (reporting bias)	High risk	Some outcomes reported in the results section of the manuscript had not been prespecified in the registered study protocol.
Other bias	Unclear risk	There were significant inequalities between the groups in levels of FSH and HDL.

Duleba 2006

Study characteristics	
Methods	**Sequence generation and allocation:** block randomisation (blocks of 10) with sealed envelopes **Blinding:** open-label **Study period:** April–August 2004
Participants	**Inclusion criteria** • PCOS diagnosis according to Rotterdam European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproduction Medicine (ASRM)-sponsored PCOS Consensus Workshop criteria for PCOS • No planned pregnancy during the study period **Exclusion criteria** • Congenital adrenal hyperplasia, endocrinopathies, androgen secreting tumours, thyroid disease, hyperprolactinaemia, diabetes mellitus • Use of any OCP or other steroids or medications that interfere with steroid hormones, ovarian functions, insulin sensitivity, or lipid metabolism within 3 months prior to start of • Contraindications to OCP **Compliance to statins:** not reported
Interventions	**Intervention(s)** • Simvastatin 20mg orally once a day plus OCP containing 20 µg ethinyl oestradioland 150 µg desogestrel **Comparator(s)** • OCP (20 µg ethinyl oestradioland 150 µg desogestrel) alone **Treatment duration:** 3 months **Comedication:** none
Outcomes	**Primary outcome(s)** • Serum total testosterone level, measured by chemiluminescence method **Secondary outcome(s)** • BMI • DHEAS • SHBG • FSH • LH • LH/FSH ratio • LDL cholesterol • HDL cholesterol • Total cholesterol • Triglycerides • Fasting insulin • Insulin AUC • Fasting glucose • Glucose AUC • Quantitative insulin sensitivity check index

Duleba 2006 *(Continued)*

	• HOMA insulin sensitivity index **Other outcome(s)** • Hirsutism measured on the Ferriman-Gallwey scale
Notes	**Country:** Poland **Setting:** Division of Fertility and Reproductive Endocrinology, Poznan University of Medical Sciences **Funding:** drugs supplied by pharmaceutical companies (i.e. simvastatin from Polfa Grodzisk Mazowiecki and OCP from Organone Polska). Supported by NIH grant. **Trial registration:** no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation used; no further details.
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes; no further details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	High risk	All findings in accordance with primary and secondary objectives; however, length of menstrual cycle and hirsutism measurement were not mentioned methods. The poster presentation of the study (Banaszewska 2005) after the cross-over phase reported that simvastatin-attributed decline in hirsutism with intervention was modest but significantly greater than with OCP alone (4% difference), and that the difference in acne was statistically insignificant.
Other bias	Low risk	The study appears to be free from other sources of bias. There were no statistically significant differences between the groups at baseline.

Mehrabian 2016

Study characteristics

Methods	**Sequence generation and allocation:** participants allocated to 3 groups randomly in 1:1:1 allocation ratio; allocation was concealed using sealed envelopes. **Blinding:** single-blind (physician) **Study period:** April 2013–November 2014

Mehrabian 2016 *(Continued)*

Participants	**Inclusion criteria**
	• PCOS diagnosis according to Rotterdam diagnostic criteria: ≥ 2 of:
	  ○ ovulatory dysfunction as oligo-ovulation or anovulation;
	  ○ biochemical or clinical evidence of hyperandrogenism; or
	  ○ polycystic ovaries as viewed by transvaginal ultrasound.
	• Age ≥ 18 years
	• Single
	• No evidence of thyroid dysfunction, Cushing's syndrome, or hyperprolactinemia
	• Normal kidney function, bilirubin level, and serum aminotransferases
	Exclusion criteria
	• Non-compliance with study protocol or unwillingness to continue study
	• Emerging side effects of drugs or contraindication
	• Smoking
	• Breast cancer
	• Use of drug that probably affects ovarian function, insulin sensitivity, or lipid profile
	• Contraindication to study drugs
	Compliance to statins: not reported

Interventions	**Intervention(s)** • Simvastatin 20 mg daily **Comparator(s)** • Flutamide 62.5 mg daily plus low-dose OCP (levonorgestrel 0.15 mg plus ethinyl oestradiol0.03 mg-daily) • Metformin 1000 mg daily **Treatment duration**: 6 months **Comedication:** none
Outcomes	**Primary outcome(s)** • Insulin resistance, defined as HOMA-IR ≥ 2.5 (HOMA-IR = fasting serum insulin (micro U/mL) × fasting plasma glucose (mg/dL)/22.5) • Fasting blood sugar • CRP • Blood pressure **Secondary outcome(s)** • BMI • Waist circumference **Other outcome(s)** • HDL cholesterol* • Triglycerides* *not prespecified in protocol
Notes	**Country:** Iran **Setting:** midwifery clinic of Al-Zahra Hospital and Beheshti Hospital, Isfahan, Iran

Mehrabian 2016 *(Continued)*

Funding: Isfahan University of Medical Sciences funded this study.

Trial registration: fa.irct.ir/trial/7999

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "[...] Each subject had been randomly given a card by the acceptance nurse. After referring to a physician, according to the subject's card, the physician had given them a sealed envelope, with one of the letter A, B, or C on it [...]" Comment: unclear if the cards were shuffled.
Allocation concealment (selection bias)	Unclear risk	Quote: "[...] Each subject had been randomly given a card by the acceptance nurse. After referring to a physician, according to the subject's card, the physician had given them a sealed envelope, with one of the letter A, B, or C on it [...]" Comment: unclear if the envelope was opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study with only physician blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single-blind study with only physician blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	8.1% loss to follow-up due to non-compliance.
Selective reporting (reporting bias)	High risk	All outcomes stated in the protocol were reported in the main study publication; however, results were reported for partial outcomes (e.g. lipid tests were reported for only triglycerides and HDL). There were no reported follow-up data on insulin resistance.
Other bias	Unclear risk	Waist circumference in simvastatin group was significantly lower than in the other 2 groups, although there were no differences in other variables including BMI.

Puurunen 2013

Study characteristics

Methods	**Sequence generation and allocation:** Computer-generated randomisation list with blocks of 6. Sequence generation and allocation of treatment was performed by a person not involve in the study directly; sealed sequentially numbered packages of study medications were prepared. **Blinding:** double-blind **Study period:** September 2007–January 2011
Participants	**Inclusion criteria**

Puurunen 2013 *(Continued)*

- PCOS diagnosis according to Rotterdam criteria 2003: ≥ 2 of:
  - oligomenorrhea;
  - hyperandrogenism; or
  - polycystic ovaries on ultrasound.
- Age 29–50 years
- Not menopausal
- Safe non-hormonal contraception

Exclusion criteria

- Type 2 diabetes mellitus
- Use of medication affecting glucose tolerance, lipid metabolism, or steroid synthesis in the preceding 3 months
- Menopause
- Regular smoking
- Abuse of alcohol
- History of ovarian drilling, oophorectomy, or hysterectomy
- Contraindication for the use of atorvastatin

Compliance to statins: not reported

Interventions	**Intervention(s)** • Atorvastatin 20 mg once daily (every evening) **Comparator(s)** • Placebo **Treatment duration:** 6 months (with follow-up at 3 months) **Comedication:** none
Outcomes	**Primary outcome(s)** • Androgen secretion (total testosterone, DHEAS, SHBG) • Glucose metabolism (fasting glucose, insulin, insulin sensitivity) **Secondary outcomes** • hs-CRP • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides • FSH • LH • WHR • BMI • Systolic blood pressure • Diastolic blood pressure • Creatinine • ALAT **Other outcome(s):** none
Notes	**Country:** Finland **Setting:** Oulu University Hospital, Oulu, Finland

Puurunen 2013 *(Continued)*

Funding: Academy of Finland, the Sigrid Jusélius Foundation, the Finnish Medical Foundation, the National Clinical Graduate School, the Research Foundation of Obstetrics and Gynecology, Oulu University Scholarship Foundation, the North Ostrobothnia Regional fund of the Finnish Cultural Foundation, the Tyyni Tani Foundation of the University of Oulu, and the Finnish-Norwegian Medical Foundation. Atorvastatin and placebo were provided by Pfizer Inc.

Trial registration:clinicaltrials.gov/ct2/show/NCT01072097; www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003584-31

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list in block of 6.
Allocation concealment (selection bias)	Low risk	Allocation carried out at the hospital pharmacy by personnel not involved in the study; they repacked the medication in closed envelopes, which were sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded to the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information.
Incomplete outcome data (attrition bias) All outcomes	High risk	> 20% attrition in both the groups. Method to handle missing data not reported. Analysis per protocol.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported in the results.
Other bias	High risk	There were inequalities between the groups in levels of glucose, insulin, and testosterone.

Raja-Khan 2011

Study characteristics

Methods	**Sequence generation and allocation:** biostatistician generated a permuted block randomisation scheme for the allocation sequence. A different person (pharmacist) did over-encapsulation of the atorvastatin and placebo. **Blinding:** double-blind **Study period:** 20 October 2006 – 8 September 2008
Participants	**Inclusion criteria** • PCOS (1990 NIH criteria) • LDL cholesterol > 100 mg/dL (cut-off according to NCEP guideline) **Exclusion criteria**

Raja-Khan 2011 *(Continued)*

- Current pregnancy or breastfeeding
- Current use of oral contraceptives or progestins
- Insulin-sensitising medications
- Thyroid disease, hyperprolinaemia, active liver disease, type 1 or type 2 diabetes

Compliance to statins: not reported

Interventions	**Intervention(s)** • Atorvastatin 60 mg/day, orally **Comparator(s)** • Placebo **Treatment duration:** 1.5 month (6 weeks) **Comedication** • Oral contraceptives (1 woman) • Antihypertensives (2 women)
Outcomes	**Primary outcome(s)** • Improvement of vascular function: brachial artery flow-mediated dilation (FMD), peak brachial artery conductance, • hs-CRP • Androgen levels: total testosterone, free testosterone, androstenedione, DHEAS **Secondary outcome(s)** • BMI • Systolic blood pressure • Diastolic blood pressure • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides • AUC insulin • Mean ovarian volume **Other outcome(s):** none
Notes	**Country:** USA **Setting:** not reported **Funding:** NIH grant number K12HD055882, "Career Development Program in Women's Health Research at Penn State," from the National Institute of Child Health and Human Development (NICHD), GCRC grant M01 RR10732 and construction grant C06 RR016499 to Pennsylvania State University, and a research grant from Pfizer. **Trial registration:** www.clinicaltrials.gov/ct2/show/NCT00529542 The trial was terminated early because of lack of funding for the required sample size.

Risk of bias

Bias	Authors' judgement	Support for judgement

Raja-Khan 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Biostatistician generated a permuted block randomisation scheme for the allocation sequence using a random number table.
Allocation concealment (selection bias)	Low risk	The atorvastatin and placebo were over-encapsulated by the pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, research co-ordinator who administered the intervention, and investigators who assessed the outcomes were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, research co-ordinator who administered the intervention, and investigators who assessed the outcomes were blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was used.
Selective reporting (reporting bias)	High risk	Study results mentioned that level of progesterone did not change significantly; however, the result was not interpreted in terms of ovulation rate.
Other bias	High risk	BMI and total testosterone differed significantly at baseline between the statin and placebo groups.

Sathyapalan 2009

Study characteristics	
Methods	**Sequence generation and allocation:** computer-generated randomisation list. Personnel not involved in the trial were responsible for labelling. **Blinding:** double-blind **Study period:** 13 July 2006–1 May 2008

Participants	**Inclusion criteria**
	
	• PCOS based on Rotterdam criteria (all 3):
	  ◦ clinical and biochemical evidence of hyperandrogenaemia (Ferriman-Gallwey score > 8; free androgen index);
	  ◦ oligomenorrhea or amenorrhoea; and
	  ◦ polycystic ovaries in transvaginal ultrasound.
	• Age 18–40 years
	• No concurrent illness
	• No medicine, OTC, or oral contraceptive products in preceding 6 months that may affect insulin sensitivity, lipid profile, or ovarian function
	• No previous statin therapy
	• Use of barrier method of contraception
	
	Exclusion criteria
	
	• Non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, or androgen-secreting tumour
	• No concurrent illness
	• Unwillingness to allow disclosure to their GPs

Sathyapalan 2009 *(Continued)*

	• No barrier or oral progesterone contraception **Compliance to statins:** 99%
Interventions	**Intervention(s)** • Atorvastatin 20 mg daily. Participants were advised not to alter their usual dietary and exercise habits. **Comparator(s)** • Placebo. Participants were advised not to alter their usual dietary and exercise habits. **Treatment duration:** 3 months **Comedication:** none
Outcomes	**Primary outcome(s)** • hs-CRP **Secondary outcome(s)** • HOMA-IR • Total testosterone • Weight • BMI • Waist • Glucose • Free androgen index • SHBG • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides • Lipid levels • Insulin levels
Notes	**Country:** UK **Setting:** not stated clearly. Presumed to be Hull and East Yorkshire's Women's and Children's hospital, UK from the address of the study authors and name of the local ethical committee mentioned in the study. **Funding:** unrestricted grant from Pfizer **Trial registration:**www.isrctn.com/ISRCTN24474824 (retrospectively registered)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was prepared (each randomisation number corresponded with 1 of the 2 possible interventions).
Allocation concealment (selection bias)	Unclear risk	Personnel not involved in the study were responsible for labelling.
Blinding of participants and personnel (performance bias)	Low risk	Reported as a double-blind trial.

Sathyapalan 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as a double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% loss to follow-up due to non-compliance.
Selective reporting (reporting bias)	High risk	All findings were in accordance with those mentioned in primary and secondary objective. However, some clinical outcomes reported in the results section (e.g. length of menstrual cycle) were not prespecified in the methodology section or protocol.
Other bias	Low risk	The study appears to be free from other sources of bias. There were no statistically significant differences between the groups at baseline.

ALAT: alanine transaminase; AUC: area under the curve; BMI: body mass index; CRP: C-reactive protein; DHEAS: dehydroepiandrosterone sulfate; FSH: follicle-stimulating hormone; GP: general practitioner; HOMA: homeostatic model assessment; HOMA-IR: homeostatic model assessment for insulin resistance; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; LH: luteinising hormone; NCEP: National Cholesterol Education Program; NIH: US National Institutes of Health; PCOS: polycystic ovary syndrome; OCP: oral contraceptive pill; OTC: over-the-counter; SD: standard deviation; SHBG: sex hormone binding globulin; sVCAM-1: soluble vascular cell adhesion molecule 1; WHR: waist-hip ratio.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akbari 2016	Non-randomised study.
Banaszewska 2010	Review article.
Celik 2012	Non-randomised study.
Economou 2011	Narrative review on hypolipidaemic treatment for PCOS.
Gao 2012	Systematic review and meta-analysis examining effect of statins in women with PCOS.
Ghazeeri 2015	RCT on effect of metformin among women with PCOS after pretreatment with simvastatin.
IRCT20140525017827N8	Wrong intervention: wormatin.
Kaya 2009	Wrong comparison: atorvastatin versus simvastatin (2 different statin derivatives) with no placebo group.
Kaya 2010	Wrong comparison: atorvastatin versus simvastatin (2 different statin derivatives) with no placebo group.
Kazerooni 2010	Quasi-randomised study.
Krysiak 2015	Prospective study examining effect of ezetimibe in women with PCOS after pretreatment with atorvastatin.
Malik 2018	Non-randomised study.

Study	Reason for exclusion
Navali 2011	Wrong study design
NCT02766803	RCT examining effect of Micronized Trans-Resveratrol in women with PCOS who are on simvastatin.
Pourmatroud 2014	RCT examining effect of statin in women who are actively trying to conceive using in-vitro fertilisation (IVF).
Rashidi 2011	RCT examining effect of statin in women who are actively trying to conceive using intracytoplasmic sperm injection (ICSI).
Sun 2015	Systematic review and meta-analysis examining effect of statins in women with PCOS.
Yang 2016	Non-randomised control study comparing effect of statins in women with PCOS.

PCOS: polycystic ovary syndrome; RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

IRCT201012285487N2

Methods	**Sequence generation and allocation:** not stated **Blinding:** double-blind **Study period:** not stated

Participants	**Inclusion criteria**
	
	• Age 20–40 years
	• PCOS, diagnosed by:
	  ◦ clinical symptoms or biochemical parameters of hyperandrogenism; and
	  ◦ irregular menstruation.
	• Normal levels of bilirubin, creatinine, BUN, SGOT, SGPT, TSH
	
	Exclusion criteria
	
	• Presence of congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, androgen secreted by tumours, thyroid disease, diabetes mellitus, hypertension, or history of cardiovascular disease
	• Use of OCP, other steroid hormones, or any drugs affecting ovarian function, insulin sensitivity, or lipid profiles
	• Pregnancy
	• Incidence of any adverse effects (liver and renal function tests elevation) during treatment
	
	Compliance to statins: not stated

Interventions	**Intervention(s)** • Metformin 1500 mg orally, once daily **Comparator(s)** • Simvastatin 20 mg orally, once daily **Treatment duration:** 3 months
Outcomes	**Primary outcome(s)***

IRCT201012285487N2 *(Continued)*

- BP
- Weight
- BMI
- Hirsutism
- Acne
- Irregular menstruation
- Prolactin
- GTT
- FSH
- LH
- Total testosterone
- Free testosterone
- SHBG
- DHEAS
- Serum Insulin
- Insulin sensitivity Index
- Triglycerides
- Total cholesterol
- HDL
- LDL
- CRP

*as reported in protocol

Secondary outcome(s): none

Other outcome(s): none

Notes	**Country:** not stated **Setting:** not stated **Funding:** not stated We were unable to find a full text report for this registered trial.

IRCT201208299626N1

Methods	**Sequence generation and allocation:** not stated **Blinding:** double-blind **Study period:** not stated
Participants	**Inclusion criteria** • PCOS (diagnostic criteria not reported) **Exclusion criteria** • Any disease in past month • Ingestion of any drug that might affect insulin level, lipids, or ovary function in past 6 months • Previous statin use • Any change in lifestyle during study • Pregnancy or lactation

IRCT201208299626N1 *(Continued)*

	Compliance to statins: not stated
Interventions	**Intervention(s)** • Atorvastatin (Razak tablet) 20 mg once daily **Comparator(s)** • OCP **Treatment duration:** 3 months
Outcomes	**Primary outcome(s)*** • Biochemical and haemostatic profile *as reported in protocol **Secondary outcome(s)*** • Alternation in biochemical and haemostatic profile *as reported in protocol **Other outcome(s):** none
Notes	**Country:** not stated **Setting:** not stated **Funding:** not stated We were unable to find a full text report for this registered trial.

PACTR201710002641118

Methods	**Sequence generation and allocation:** not stated **Blinding:** double-blind **Study period:** not stated

Participants	**Inclusion criteria**
	• Age 18–35 years
	• PCOS based on the 3 diagnostic criteria of the Rotterdam consensus, namely:
	  ◦ clinical and biochemical evidence of hyperandrogenism (Ferriman-Gallwey score, free androgen index);
	  ◦ oligomenorrhoea or amenorrhoea; and
	  ◦ polycystic ovaries on transabdominal ultrasound.
	• Unmarried women with no plan to marry at least till the end of study period
	• Fasting insulin > 15 mU/L
	Exclusion criteria
	• Smoking
	• Alcohol abuse
	• Chronic disease history
	• Application of hormone or lipid metabolism regulation drugs within 2 months
	• Pregnancy or lactation

PACTR201710002641118 *(Continued)*

	Compliance to statins: not stated
Interventions	Not stated
Outcomes	Not stated
Notes	**Country:** Egypt **Setting:** Tertiary care clinic **Funding:** Emaduldin Seyam; Minia University, Minia, Egypt, Pincode:1357 We were unable to find a full text report for this registered trial.

Seyam 2017

Methods	**Sequence generation and allocation:** computer-generated randomisation list; a person who were not involved in the study was responsible for labelling. Allocation concealment not reported. **Blinding:** double-blind **Study period:** January 2013–December 2016

Participants	**Inclusion criteria**
	• PCOS based on Rotterdam criteria:
	  ◦ clinical and biochemical evidence of hyperandrogenism and at least 1 of:
	  ▪ oligomenorrhea or amenorrhoea; or
	  ▪ polycystic ovaries on transabdominal ultrasound.
	• Young single, unmarried
	Exclusion criteria
	• No concurrent illness
	• Use of any medication affecting insulin sensitivity, lipids or ovarian function including OCP for the preceding 6 months
	• No statin therapy in the past
	• 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, and androgen-secreting tumours
	Compliance to statins: pill count method

Interventions	**Intervention(s)** • Simvastatin 20 mg once daily **Comparator(s)** • Placebo **Treatment Duration:** 6 months (with follow-up at 3 months)
Outcomes	**Primary outcome(s)** • Serum androgens: total testosterone, free testosterone, DHEAS, SHBG • PCOS clinical, hormonal, and metabolic abnormalities **Secondary outcome(s)** • Spontaneous menses

Seyam 2017 *(Continued)*

- Spontaneous ovulation
- Volume of ovaries
- BMI
- WHR
- Hirsutism (FG score)
- Acne (score)
- LH
- FSH
- LH/FSH ratio
- Prolactin
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Fasting glucose
- Fasting insulin
- Insulin sensitivity index

Notes	**Country:** Egypt **Setting:** tertiary care clinic **Funding:** none declared There are concerns regarding the validity of study data. Overlap with Seyam 2018. Study currently under investigation by publisher's ethics team.

Seyam 2018

Methods	**Sequence generation and allocation:** computer-generated randomised list generated by personnel not involved in the trial; allocation concealment by an independent pharmacist **Blinding:** double-blind **Study period:** January 2013–December 2017

Participants	**Inclusion criteria**
	
	• PCOS based on Rotterdam criteria (all 3):
	  ◦ clinical and biochemical evidence of hyperandrogenism (Ferriman–Gallwey score and free androgen index);
	  ◦ oligomenorrhoea or amenorrhoea; and
	  ◦ polycystic ovaries on ultrasound.
	• Single unmarried
	
	Exclusion criteria
	
	• Use of any medication affecting insulin sensitivity, lipids, or ovarian function (including OCP) in 6 months before the start of study
	• Concurrent illness
	• 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, and androgen-secreting tumours
	
	Compliance to statins: pill count method

Interventions	**Intervention(s)**

Seyam 2018 *(Continued)*

	• Simvastatin 20 mg once per day + metformin 500 3 times per day **Comparator(s)** • Simvastatin 20 mg once per day • Metformin 500 3 times per day **Treatment duration:** 12 months
Outcomes	**Primary outcome(s)** • Serum androgens: total testosterone, free testosterone, DHEAS, SHBG • Insulin resistance • PCOS clinical, hormonal, metabolic abnormalities **Secondary outcome(s):** none **Other outcome(s)** • Spontaneous menses • Spontaneous ovulation • Volume of ovaries • BMI • WHR • Hirsutism (FG score) • Acne (score) • LH • FSH • LH/FSH ratio • Prolactin • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglycerides • Fasting glucose • Fasting insulin • Insulin sensitivity index
Notes	**Country:** Egypt **Setting:** tertiary care clinic **Funding:** none declared There are concerns regarding the validity of study data. Overlap with Seyam 2017. Study currently under investigation by publisher's ethics team.

Shi X 2013

Methods	**Sequence generation and allocation:** not stated **Blinding:** not stated **Study period:** not stated
Participants	**Inclusion criteria**

Shi X 2013 *(Continued)*

	• Age 23–39 years • PCOS (Rotterdam criteria 2003) **Exclusion criteria** • Use of other steroid hormones or any drugs affecting ovarian function or insulin sensitivity in the 3 months before start of study
Interventions	**Intervention(s)** • Metformin 500 mg orally 3 times per day **Comparator(s)** • Metformin 500 mg, orally 3 times per day + simvastatin 20 mg orally once per day **Treatment duration:** 4-month
Outcomes	**Primary outcome(s)** • Height • Body weight • BMI • Fasting blood glucose • Fasting insulin • FSH • LH • Free testosterone • Total cholesterol • HDL • LDL • Triglycerides **Secondary outcome(s):** none **Other outcome(s):** none
Notes	**Country:** not stated **Setting:** not stated **Funding:** not stated The published data are incomplete; we have contacted study authors for more information but have not received a response.

Wan Y 2014

Methods	**Sequence generation and allocation:** not stated **Blinding:** not stated **Study period:** not stated
Participants	**Inclusion criteria** • Age 23–42 years • PCOS (diagnostic criteria not stated)

Wan Y 2014 *(Continued)*

	Exclusion criteria • Concurrent illness • Use of prescription or over-the counter medication that might affect insulin sensitivity, lipids, or ovarian function, including hormonal contraceptives, in the preceding 6 months • 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease, or androgen-secreting tumours
Interventions	**Intervention(s)** • Metformin 500 mg orally 3 times per day **Comparator(s)** • Metformin 500 mg orally 3 times per day + simvastatin 20 mg orally once per day **Treatment duration:** 63 days
Outcomes	**Primary outcome(s)*** • Blood glucose parameters include (fasting blood glucose, fasting insulin) • Blood lipid parameters (triacylglycerol, total cholesterol, HDL and LDL cholesterol) • Sex hormones (testosterone, LH, LH/FSH) *as reported in the protocol **Secondary outcome(s):** none **Other outcome(s):** none
Notes	**Country:** not stated **Setting:** not stated **Funding:** not stated The published data are incomplete; we have contacted study authors for more information but have not received a response.

Xiao L 2014

Methods	We were unable to find a study protocol or full-text report.
Participants	
Interventions	
Outcomes	
Notes	

BP: blood pressure; BMI: body mass index; BUN: blood urea nitrogen; CRP: C-reactive protein; DHEAS: dehydroepiandrosterone sulfate; FG score: Ferriman-Gallwey score; FSH: follicle-stimulating hormone; GTT: glucose tolerance test; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LH: luteinising hormone; OCP: oral contraceptive pill; RCT: randomised controlled trial; SHBG: sex hormone binding globulin; WHR: waist-hip ratio.

DATA AND ANALYSES

Comparison 1. Statin versus placebo

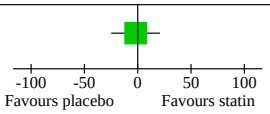
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resumption of menstrual regularity (menstrual cycle length in days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2 Body mass index (kg/m^2)	3	85	Mean Difference (IV, Fixed, 95% CI)	1.06 [-1.87, 3.99]
1.2.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	2.40 [-6.02, 10.82]
1.2.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-4.64, 3.12]
1.2.3 After 6 months' treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	3.90 [-1.38, 9.18]
1.3 Waist circumference (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Waist-hip ratio	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Improvement in testosterone level (nmol/L)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Random, 95% CI)	0.06 [-0.72, 0.84]
1.5.2 After 3 months' treatment	2	65	Mean Difference (IV, Random, 95% CI)	-0.53 [-1.61, 0.54]
1.5.3 After 6 months' treatment	1	28	Mean Difference (IV, Random, 95% CI)	0.10 [-0.43, 0.63]
1.6 Total cholesterol (mmol/L)	3	85	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-1.64, -0.97]
1.6.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.56 [-2.17, -0.95]
1.6.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.75, -0.65]
1.6.3 After 6 months' treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.78, -0.62]
1.7 Low-density lipoprotein (LDL) cholesterol (mmol/L)	3	85	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.38, -0.81]
1.7.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.29 [-1.82, -0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.34, -0.46]
1.7.3 After 6 months' treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.75, -0.65]
1.8 High-density lipoprotein (HDL) cholesterol (mmol/L)	3	85	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.15, 0.15]
1.8.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.22, 0.26]
1.8.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.28, 0.24]
1.8.3 After 6 months' treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.26, 0.26]
1.9 Triglycerides (mmol/L)	3	85	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.60, -0.18]
1.9.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-0.91, -0.23]
1.9.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.61 [-1.20, -0.02]
1.9.3 After 6 months' treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.50, 0.10]
1.10 Improvement in high-sensitivity C-reactive protein (nmol/L)	3	84	Mean Difference (IV, Fixed, 95% CI)	-7.76 [-20.99, 5.48]
1.10.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Fixed, 95% CI)	-16.19 [-69.27, 36.89]
1.10.2 After 3 months' treatment	1	37	Mean Difference (IV, Fixed, 95% CI)	-21.91 [-58.16, 14.34]
1.10.3 After 6 months' treatment	1	27	Mean Difference (IV, Fixed, 95% CI)	-4.76 [-19.52, 10.00]
1.11 Fasting insulin (µIU/L)	3	85	Mean Difference (IV, Random, 95% CI)	-0.31 [-5.18, 4.57]
1.11.1 After 6 weeks' treatment	1	20	Mean Difference (IV, Random, 95% CI)	2.50 [-2.12, 7.12]
1.11.2 After 3 months' treatment	1	37	Mean Difference (IV, Random, 95% CI)	-5.20 [-10.96, 0.56]
1.11.3 After 6 months' treatment	1	28	Mean Difference (IV, Random, 95% CI)	1.50 [-5.30, 8.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Homeostatic model assessment for insulin resistance	1	37	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.35, 0.15]
1.13 Intravenous glucose tolerance test (IVGTT) insulin sensitivity	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: Statin versus placebo, Outcome 1: Resumption of menstrual regularity (menstrual cycle length in days)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Sathyapalan 2009 (1)	50	26.153394	19	52	42.426407	18	-2.00 [-24.86 , 20.86]



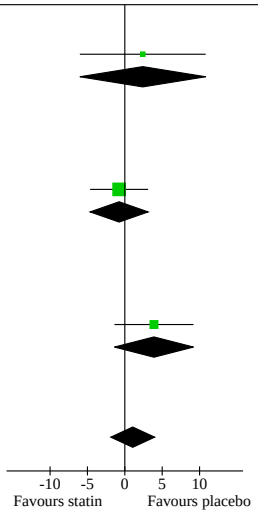
Test for subgroup differences: Not applicable

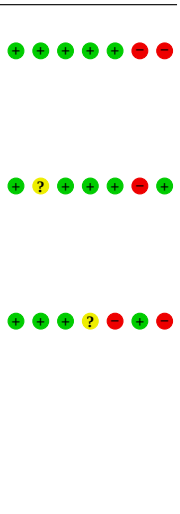
Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.2. Comparison 1: Statin versus placebo, Outcome 2: Body mass index (kg/m^2)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 After 6 weeks' treatment								
Raja-Khan 2011	38.2	8.4	9	35.8	10.8	11	12.1%	2.40 [-6.02 , 10.82]
Subtotal (95% CI)			**9**			**11**	**12.1%**	**2.40 [-6.02 , 10.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.58)								
1.2.2 After 3 months' treatment								
Sathyapalan 2009	33.16	6.102459	19	33.92	5.939697	18	57.1%	-0.76 [-4.64 , 3.12]
Subtotal (95% CI)			**19**			**18**	**57.1%**	**-0.76 [-4.64 , 3.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
1.2.3 After 6 months' treatment								
Puurunen 2013	30.7	9.2	15	26.8	4.6	13	30.8%	3.90 [-1.38 , 9.18]
Subtotal (95% CI)			**15**			**13**	**30.8%**	**3.90 [-1.38 , 9.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.45 (P = 0.15)								
Total (95% CI)			**43**			**42**	**100.0%**	**1.06 [-1.87 , 3.99]**
Heterogeneity: Chi² = 2.05, df = 2 (P = 0.36); I² = 3%								
Test for overall effect: Z = 0.71 (P = 0.48)								
Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.5%								

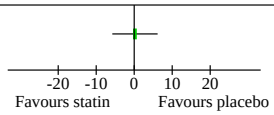


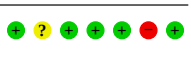


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Statin versus placebo, Outcome 3: Waist circumference (cm)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Sathyapalan 2009 (1)	98.9	9.589578	19	98.7	8.909545	18	0.20 [-5.76 , 6.16]



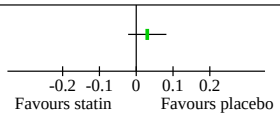


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Statin versus placebo, Outcome 4: Waist-hip ratio

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Puurunen 2013 (1)	0.88	0.08	15	0.85	0.06	13	0.03 [-0.02 , 0.08]

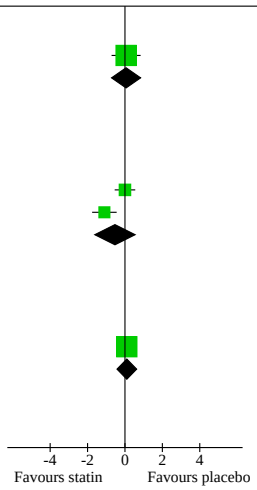


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Statin versus placebo, Outcome 5: Improvement in testosterone level (nmol/L)

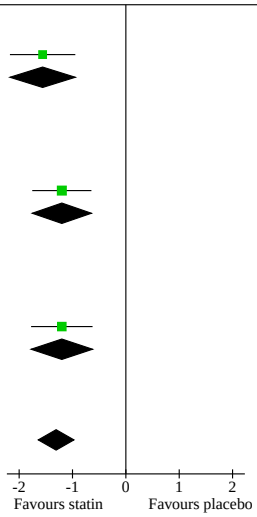
Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 After 6 weeks' treatment								
Raja-Khan 2011	-0.52	0.871638	9	-0.58	0.893111	11	100.0%	0.06 [-0.72 , 0.84]
Subtotal (95% CI)			**9**			**11**	**100.0%**	**0.06 [-0.72 , 0.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.5.2 After 3 months' treatment								
Puurunen 2013	0	0.975114	15	0	0.446802	13	51.4%	0.00 [-0.55 , 0.55]
Sathyapalan 2009	-1.2	0.912892	19	-0.1	1.105998	18	48.6%	-1.10 [-1.76 , -0.44]
Subtotal (95% CI)			**34**			**31**	**100.0%**	**-0.53 [-1.61 , 0.54]**
Heterogeneity: Tau² = 0.51; Chi² = 6.35, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 0.97 (P = 0.33)								
1.5.3 After 6 months' treatment								
Puurunen 2013	-0.1	0.975114	15	-0.2	0.330965	13	100.0%	0.10 [-0.43 , 0.63]
Subtotal (95% CI)			**15**			**13**	**100.0%**	**0.10 [-0.43 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								

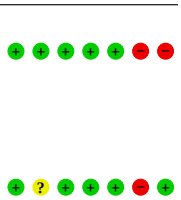


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Statin versus placebo, Outcome 6: Total cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 After 6 weeks' treatment								
Raja-Khan 2011	3.43	0.51	9	4.99	0.87	11	29.8%	-1.56 [-2.17 , -0.95]
Subtotal (95% CI)			**9**			**11**	**29.8%**	**-1.56 [-2.17 , -0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.99 (P < 0.00001)								
1.6.2 After 3 months' treatment								
Sathyapalan 2009	3.4	0.87178	19	4.6	0.848528	18	36.4%	-1.20 [-1.75 , -0.65]
Subtotal (95% CI)			**19**			**18**	**36.4%**	**-1.20 [-1.75 , -0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.24 (P < 0.0001)								
1.6.3 After 6 months' treatment								
Puurunen 2013	3.6	0.6	15	4.8	0.9	13	33.8%	-1.20 [-1.78 , -0.62]
Subtotal (95% CI)			**15**			**13**	**33.8%**	**-1.20 [-1.78 , -0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.08 (P < 0.0001)								
Total (95% CI)			**43**			**42**	**100.0%**	**-1.31 [-1.64 , -0.97]**
Heterogeneity: Chi² = 0.93, df = 2 (P = 0.63); I² = 0%								
Test for overall effect: Z = 7.66 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.93, df = 2 (P = 0.63), I² = 0%								

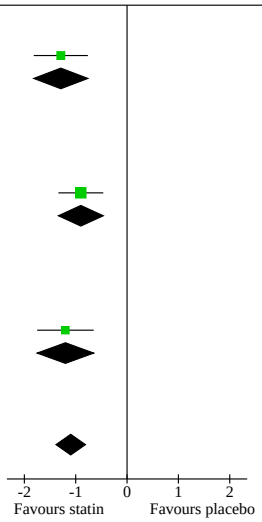


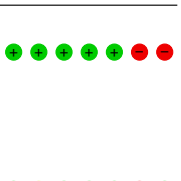


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Statin versus placebo, Outcome 7: Low-density lipoprotein (LDL) cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 After 6 weeks' treatment								
Raja-Khan 2011	1.78	0.5	9	3.07	0.7	11	29.6%	-1.29 [-1.82 , -0.76]
Subtotal (95% CI)			**9**			**11**	**29.6%**	**-1.29 [-1.82 , -0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.80 (P < 0.00001)								
1.7.2 After 3 months' treatment								
Sathyapalan 2009	1.8	0.87	19	2.7	0.42	18	43.2%	-0.90 [-1.34 , -0.46]
Subtotal (95% CI)			**19**			**18**	**43.2%**	**-0.90 [-1.34 , -0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.04 (P < 0.0001)								
1.7.3 After 6 months' treatment								
Puurunen 2013	1.8	0.5	15	3	0.9	13	27.2%	-1.20 [-1.75 , -0.65]
Subtotal (95% CI)			**15**			**13**	**27.2%**	**-1.20 [-1.75 , -0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.27 (P < 0.0001)								
Total (95% CI)			**43**			**42**	**100.0%**	**-1.10 [-1.38 , -0.81]**
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%								
Test for overall effect: Z = 7.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.43, df = 2 (P = 0.49), I² = 0%								

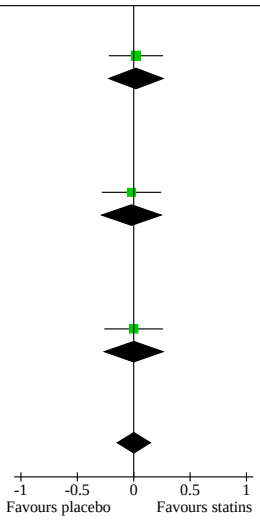


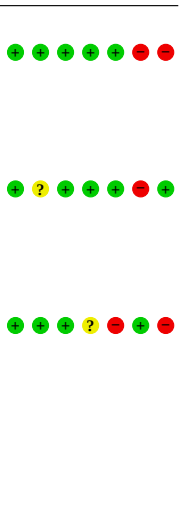


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Statin versus placebo, Outcome 8: High-density lipoprotein (HDL) cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 After 6 weeks' treatment								
Raja-Khan 2011	1.24	0.31	9	1.22	0.22	11	37.2%	0.02 [-0.22 , 0.26]
Subtotal (95% CI)			**9**			**11**	**37.2%**	**0.02 [-0.22 , 0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.16 (P = 0.87)								
1.8.2 After 3 months' treatment								
Sathyapalan 2009	1.08	0.43589	19	1.1	0.381838	18	31.0%	-0.02 [-0.28 , 0.24]
Subtotal (95% CI)			**19**			**18**	**31.0%**	**-0.02 [-0.28 , 0.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.8.3 After 6 months' treatment								
Puurunen 2013	1.5	0.4	15	1.5	0.3	13	31.9%	0.00 [-0.26 , 0.26]
Subtotal (95% CI)			**15**			**13**	**31.9%**	**0.00 [-0.26 , 0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**43**			**42**	**100.0%**	**0.00 [-0.15 , 0.15]**
Heterogeneity: Chi² = 0.05, df = 2 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.02 (P = 0.99)								
Test for subgroup differences: Chi² = 0.05, df = 2 (P = 0.98), I² = 0%								

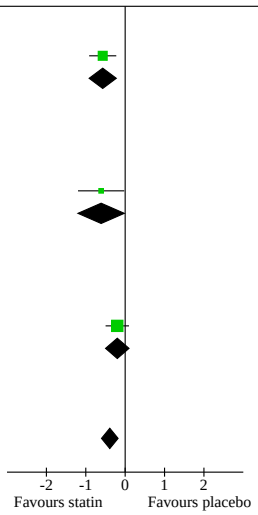




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Statin versus placebo, Outcome 9: Triglycerides (mmol/L)

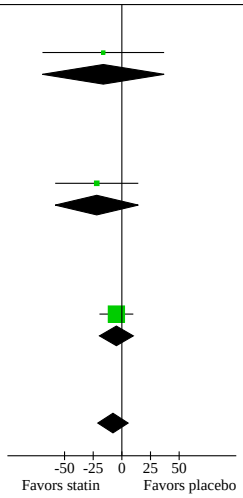
Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
1.9.1 After 6 weeks' treatment									
Raja-Khan 2011	0.89	0.27	9	1.46	0.5	11	37.2%	-0.57 [-0.91 , -0.23]	+ + + + + - -
Subtotal (95% CI)			**9**			**11**	**37.2%**	**-0.57 [-0.91 , -0.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.25 (P = 0.001)									
1.9.2 After 3 months' treatment									
Sathyapalan 2009	1.08	0.566657	19	1.69	1.145513	18	12.8%	-0.61 [-1.20 , -0.02]	+ ? + + + - +
Subtotal (95% CI)			**19**			**18**	**12.8%**	**-0.61 [-1.20 , -0.02]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.04 (P = 0.04)									
1.9.3 After 6 months' treatment									
Puurunen 2013	0.9	0.4	15	1.1	0.4	13	50.0%	-0.20 [-0.50 , 0.10]	+ + + ? - + -
Subtotal (95% CI)			**15**			**13**	**50.0%**	**-0.20 [-0.50 , 0.10]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.32 (P = 0.19)									
Total (95% CI)			**43**			**42**	**100.0%**	**-0.39 [-0.60 , -0.18]**	
Heterogeneity: Chi² = 3.16, df = 2 (P = 0.21); I² = 37%									
Test for overall effect: Z = 3.64 (P = 0.0003)									
Test for subgroup differences: Chi² = 3.16, df = 2 (P = 0.21), I² = 36.7%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Statin versus placebo, Outcome 10: Improvement in high-sensitivity C-reactive protein (nmol/L)

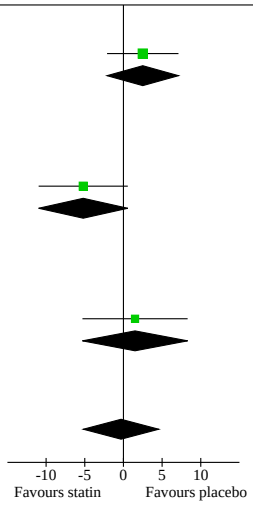
Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
1.10.1 After 6 weeks' treatment									
Raja-Khan 2011	40.96	51.43	9	57.15	69.53	11	6.2%	-16.19 [-69.27 , 36.89]	+ + + + + - -
Subtotal (95% CI)			**9**			**11**	**6.2%**	**-16.19 [-69.27 , 36.89]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.60 (P = 0.55)									
1.10.2 After 3 months' treatment									
Sathyapalan 2009	32.38	45.681261	19	54.29	64.657844	18	13.3%	-21.91 [-58.16 , 14.34]	+ ? + + + - +
Subtotal (95% CI)			**19**			**18**	**13.3%**	**-21.91 [-58.16 , 14.34]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.18 (P = 0.24)									
1.10.3 After 6 months' treatment									
Puurunen 2013	12.38	19.05	14	17.14	20	13	80.4%	-4.76 [-19.52 , 10.00]	+ + + ? - + -
Subtotal (95% CI)			**14**			**13**	**80.4%**	**-4.76 [-19.52 , 10.00]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.63 (P = 0.53)									
Total (95% CI)			**42**			**42**	**100.0%**	**-7.76 [-20.99 , 5.48]**	
Heterogeneity: Chi² = 0.84, df = 2 (P = 0.66); I² = 0%									
Test for overall effect: Z = 1.15 (P = 0.25)									
Test for subgroup differences: Chi² = 0.84, df = 2 (P = 0.66), I² = 0%									

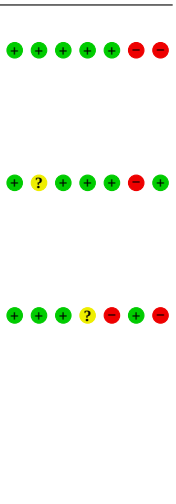


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.11. Comparison 1: Statin versus placebo, Outcome 11: Fasting insulin (µIU/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 After 6 weeks' treatment								
Raja-Khan 2011	1.4	5.203807	9	-1.1	5.284239	11	39.3%	2.50 [-2.12 , 7.12]
Subtotal (95% CI)			**9**			**11**	**39.3%**	**2.50 [-2.12 , 7.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.11.2 After 3 months' treatment								
Sathyapalan 2009	12.4	7.410128	19	17.6	10.182338	18	32.8%	-5.20 [-10.96 , 0.56]
Subtotal (95% CI)			**19**			**18**	**32.8%**	**-5.20 [-10.96 , 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.77 (P = 0.08)								
1.11.3 After 6 months' treatment								
Puurunen 2013	1.4	12.261153	15	-0.1	5.113405	13	27.8%	1.50 [-5.30 , 8.30]
Subtotal (95% CI)			**15**			**13**	**27.8%**	**1.50 [-5.30 , 8.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
Total (95% CI)			**43**			**42**	**100.0%**	**-0.31 [-5.18 , 4.57]**
Heterogeneity: Tau² = 10.17; Chi² = 4.44, df = 2 (P = 0.11); I² = 55%								
Test for overall effect: Z = 0.12 (P = 0.90)								
Test for subgroup differences: Chi² = 4.44, df = 2 (P = 0.11), I² = 54.9%								

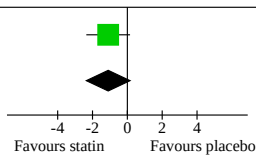




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: Statin versus placebo, Outcome 12: Homeostatic model assessment for insulin resistance

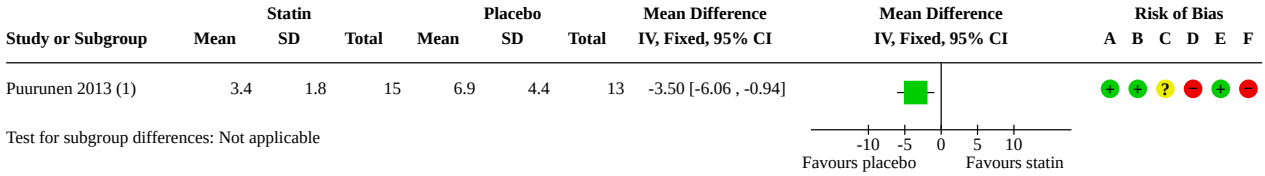
Study or Subgroup	Statin Mean	Statin SD	Statin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Sathyapalan 2009 (1)	2.7	1.74356	19	3.8	2.12132	18	100.0%	-1.10 [-2.35 , 0.15]
Total (95% CI)			**19**			**18**	**100.0%**	**-1.10 [-2.35 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.72 (P = 0.09)								
Test for subgroup differences: Not applicable								



Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.13. Comparison 1: Statin versus placebo, Outcome 13: Intravenous glucose tolerance test (IVGTT) insulin sensitivity



Test for subgroup differences: Not applicable

Footnotes
(1) After 6 months' treatment

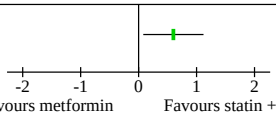
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 2. Statin plus metformin versus metformin alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Resumption of menstrual regularity (spontaneous menses per 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Body mass index (kg/m^2)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3 Improvement in hirsutism (Ferriman-Gallwey score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4 Improvement in acne severity (score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.5 Improvement in testosterone level (nmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.6 Total cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7 Low-density lipoprotein (LDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.8 High-density lipoprotein (HDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.9 Triglyceride levels (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.10 Fasting insulin (µIU/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Statin plus metformin versus metformin alone, Outcome 1: Resumption of menstrual regularity (spontaneous menses per 6 months)

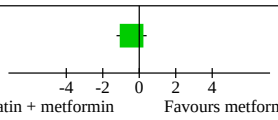
Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011	1.7	1.1	36	1.1	1.1	33	0.60 [0.08 , 1.12]		+ + − − − ?



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.2. Comparison 2: Statin plus metformin versus metformin alone, Outcome 2: Body mass index (kg/m²)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-1.35	2.3	36	-0.93	1	33	-0.42 [-1.25 , 0.41]		+ + − − − ?

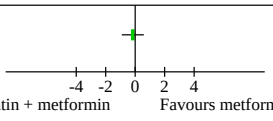


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.3. Comparison 2: Statin plus metformin versus metformin alone, Outcome 3: Improvement in hirsutism (Ferriman-Gallwey score)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-1	0.9	36	-0.84	2.010597	33	-0.16 [-0.91 , 0.59]		+ + − − − ?

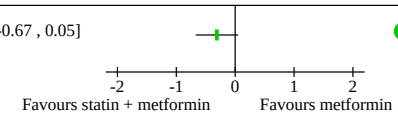


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.4. Comparison 2: Statin plus metformin versus metformin alone, Outcome 4: Improvement in acne severity (score)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Banaszewska 2011 (1)	-1.06	0.84	36	-0.75	0.689348	33	-0.31 [-0.67 , 0.05]	+	+	−	−	−	?

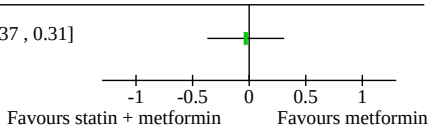


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.5. Comparison 2: Statin plus metformin versus metformin alone, Outcome 5: Improvement in testosterone level (nmol/L)

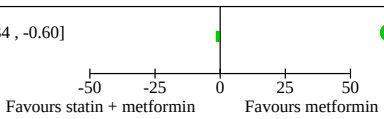
Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Banaszewska 2011 (1)	-0.55	0.62	36	-0.52	0.8	33	-0.03 [-0.37 , 0.31]



Footnotes
(1) After 6 months' treatment

Analysis 2.6. Comparison 2: Statin plus metformin versus metformin alone, Outcome 6: Total cholesterol (mmol/L)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Banaszewska 2011 (1)	-0.9	0.87	36	0.07	0.69	33	-0.97 [-1.34 , -0.60]	+	+	−	−	−	?

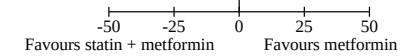


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.7. Comparison 2: Statin plus metformin versus metformin alone, Outcome 7: Low-density lipoprotein (LDL) cholesterol (mmol/L)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.83	0.69	36	0.06	0.63	33	-0.89 [-1.20 , -0.58]		+ + − − − ?

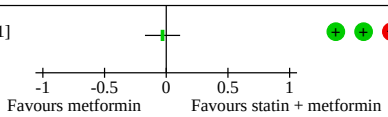


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.8. Comparison 2: Statin plus metformin versus metformin alone, Outcome 8: High-density lipoprotein (HDL) cholesterol (mmol/L)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.02	0.28	36	0.01	0.32	33	-0.03 [-0.17 , 0.11]		+ + − − − ?

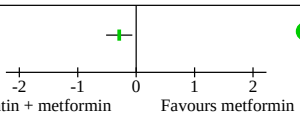


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.9. Comparison 2: Statin plus metformin versus metformin alone, Outcome 9: Triglyceride levels (mmol/L)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.15	0.48	36	0.14	0.47	33	-0.29 [-0.51 , -0.07]		+ + − − − ?

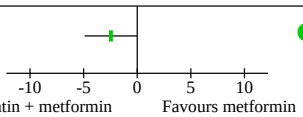


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.10. Comparison 2: Statin plus metformin versus metformin alone, Outcome 10: Fasting insulin (µIU/L)

Study or Subgroup	Statin + metformin Mean	SD	Total	Metformin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-1.73	4.56	36	0.72	5.74	33	-2.45 [-4.91 , 0.01]	+ + − − − ?



Footnotes
(1) After 6 months' treatment

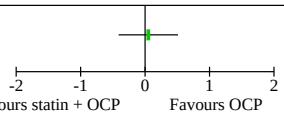
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 3. Statin plus oral contraceptive pill (OCP) versus OCP alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Body mass index (kg/m^2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2 Improvement in hirsutism (Ferriman-Gallwey score)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.41, 0.17]
3.3 Improvement in testosterone level (nmol/L)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.38, -0.26]
3.4 Total cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 Low-density lipoprotein (LDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 High-density lipoprotein (HDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7 Triglyceride levels (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8 Fasting insulin (µIU/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9 Homeostatic model assessment (HOMA) for insulin resistance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 1: Body mass index (kg/m^2)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	0.09	0.556525	24	0.04	1.006482	24	0.05 [-0.41 , 0.51]		? ? − + − +



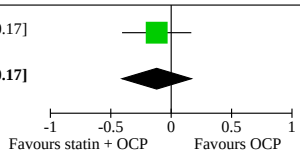
Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.2. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 2: Improvement in hirsutism (Ferriman-Gallwey score)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	-0.25	0.529452	24	-0.13	0.482673	24	100.0%	-0.12 [-0.41 , 0.17]		? ? − + − +
Total (95% CI)			**24**			**24**	**100.0%**	**-0.12 [-0.41 , 0.17]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



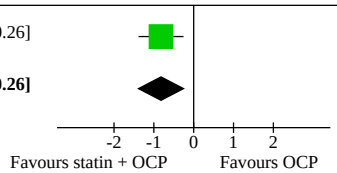
Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.3. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 3: Improvement in testosterone level (nmol/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Duleba 2006 (1)	-1.2	0.923595	24	-0.38	1.065687	24	100.0%	-0.82 [-1.38 , -0.26]	
Total (95% CI)			**24**			**24**	**100.0%**	**-0.82 [-1.38 , -0.26]**	

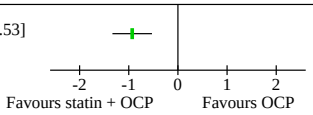
Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)
Test for subgroup differences: Not applicable



Footnotes
(1) After 3 months' treatment

Analysis 3.4. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 4: Total cholesterol (mmol/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	-0.53	0.698617	24	0.4	0.722299	24	-0.93 [-1.33 , -0.53]		? ? − + − +

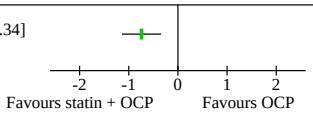


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.5. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 5: Low-density lipoprotein (LDL) cholesterol (mmol/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	-0.67	0.817026	24	0.07	0.568366	24	-0.74 [-1.14 , -0.34]		? ? − + − +

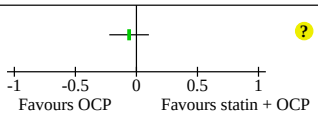


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.6. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 6: High-density lipoprotein (HDL) cholesterol (mmol/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	0.15	0.319706	24	0.21	0.24866	24	-0.06 [-0.22 , 0.10]		? ? − + − +

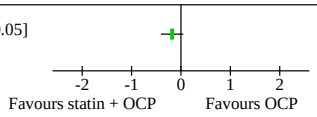


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.7. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 7: Triglyceride levels (mmol/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	0.04	0.296024	24	0.22	0.485479	24	-0.18 [-0.41 , 0.05]		? ? − + − +

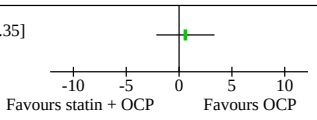


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.8. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 8: Fasting insulin (µIU/L)

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Duleba 2006 (1)	1.6	4.499566	24	1	5.210024	24	0.60 [-2.15 , 3.35]		? ? − + − +

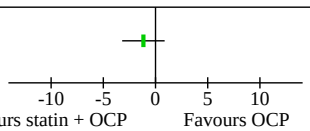


Footnotes
(1) After 3 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.9. Comparison 3: Statin plus oral contraceptive pill (OCP) versus OCP alone, Outcome 9: Homeostatic model assessment (HOMA) for insulin resistance

Study or Subgroup	Statin + OCP Mean	SD	Total	OCP Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Duleba 2006 (1)	-1.49	2.924718	24	-0.33	4.156178	24	-1.16 [-3.19 , 0.87]	



Footnotes
(1) After 3 months' treatment

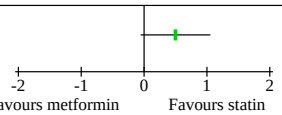
Comparison 4. Statin versus metformin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Resumption of menstrual regularity (spontaneous menses per 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Body mass index (kg/m^2)	2	129	Mean Difference (IV, Random, 95% CI)	-0.14 [-1.53, 1.25]
4.3 Waist circumference (cm)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.4 Improvement in hirsutism (Ferriman-Gallwey score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5 Improvement in acne severity (score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6 Improvement in testosterone level (nmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7 Total cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8 Low-density lipoprotein (LDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9 High-density lipoprotein (HDL) cholesterol (mmol/L)	2	129	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.02, 0.02]
4.10 Triglyceride levels (mmol/L)	2	129	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.29, -0.10]
4.11 High-sensitivity C-reactive protein (nmol/L)	1	68	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-2.60, -0.64]
4.12 Fasting insulin (µIU/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Statin versus metformin, Outcome 1: Resumption of menstrual regularity (spontaneous menses per 6 months)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	1.6	1.058301	28	1.1	1.148913	33	0.50 [-0.05 , 1.05]		+ + − − − ?



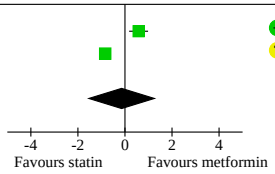
Footnotes
(1) After 6 months' treatment

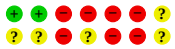
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.2. Comparison 4: Statin versus metformin, Outcome 2: Body mass index (kg/m²)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Random, 95% CI
Banaszewska 2011 (1)	-0.35	0.793725	28	-0.93	0.804239	33	49.2%	0.58 [0.18 , 0.98]
Mehrabian 2016 (1)	-1.13	0.391	34	-0.29	0.356	34	50.8%	-0.84 [-1.02 , -0.66]
Total (95% CI)			**62**			**67**	**100.0%**	**-0.14 [-1.53 , 1.25]**

Heterogeneity: Tau² = 0.98; Chi² = 40.07, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



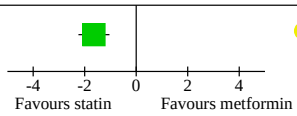


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.3. Comparison 4: Statin versus metformin, Outcome 3: Waist circumference (cm)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Random, 95% CI
Mehrabian 2016 (1)	-2.79	1.61	34	-1.15	0.784	34	-1.64 [-2.24 , -1.04]

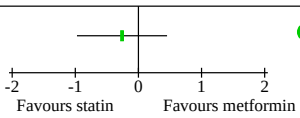


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.4. Comparison 4: Statin versus metformin, Outcome 4: Improvement in hirsutism (Ferriman-Gallwey score)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI
Banaszewska 2011 (1)	-1.1	0.52915	28	-0.84	2.010597	33	-0.26 [-0.97 , 0.45]

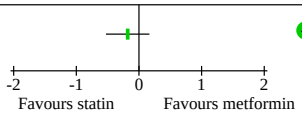


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.5. Comparison 4: Statin versus metformin, Outcome 5: Improvement in acne severity (score)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.93	0.687895	28	-0.75	0.689348	33	-0.18 [-0.53 , 0.17]		+ + − − − ?

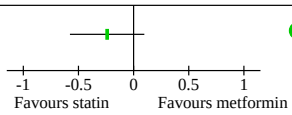


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.6. Comparison 4: Statin versus metformin, Outcome 6: Improvement in testosterone level (nmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Banaszewska 2011 (1)	-0.76	0.52915	28	-0.52	0.804239	33	-0.24 [-0.58 , 0.10]		+ + − − − − ?

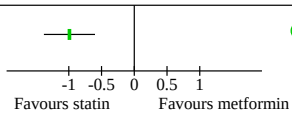


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.7. Comparison 4: Statin versus metformin, Outcome 7: Total cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Banaszewska 2011 (1)	-0.92	0.84	28	0.07	0.69	33	-0.99 [-1.38 , -0.60]		+ + − − − − ?

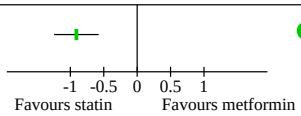


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.8. Comparison 4: Statin versus metformin, Outcome 8: Low-density lipoprotein (LDL) cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.85	0.69	28	0.06	0.63	33	-0.91 [-1.24 , -0.58]		+ + − − − ?



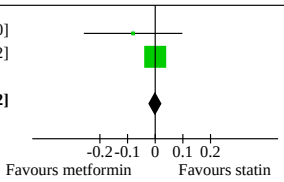
Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.9. Comparison 4: Statin versus metformin, Outcome 9: High-density lipoprotein (HDL) cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Banaszewska 2011 (1)	-0.07	0.38	28	0.01	0.32	33	1.4%	-0.08 [-0.26 , 0.10]		+ + − − − ?
Mehrabian 2016 (1)	-0.01	0.04	34	-0.01	0.05	34	98.6%	0.00 [-0.02 , 0.02]		? ? ? − − ?
Total (95% CI)			**62**			**67**	**100.0%**	**-0.00 [-0.02 , 0.02]**		

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: Not applicable



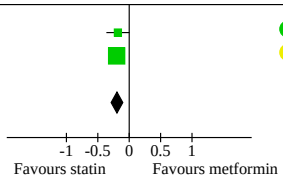
Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.10. Comparison 4: Statin versus metformin, Outcome 10: Triglyceride levels (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI
Banaszewska 2011 (1)	-0.04	0.24	28	0.14	0.47	33	25.5%	-0.18 [-0.36 , 0.00]
Mehrabian 2016 (1)	-0.28	0.3	34	-0.08	0.11	34	74.5%	-0.20 [-0.31 , -0.09]
Total (95% CI)			**62**			**67**	**100.0%**	**-0.19 [-0.29 , -0.10]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Not applicable



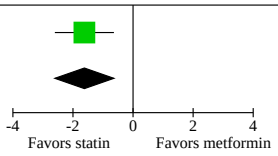
Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.11. Comparison 4: Statin versus metformin, Outcome 11: High-sensitivity C-reactive protein (nmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI
Mehrabian 2016 (1)	-2	2.54	34	-0.38	1.45	34	100.0%	-1.62 [-2.60 , -0.64]
Total (95% CI)			**34**			**34**	**100.0%**	**-1.62 [-2.60 , -0.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.23 (P = 0.001)
Test for subgroup differences: Not applicable

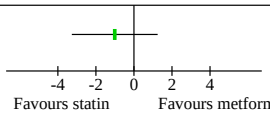


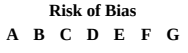
Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.12. Comparison 4: Statin versus metformin, Outcome 12: Fasting insulin (µIU/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	Metformin Mean	Metformin SD	Metformin Total	Mean Difference IV, Fixed, 95% CI
Banaszewska 2011 (1)	-0.29	3.01616	28	0.72	5.74456	33	-1.01 [-3.27 , 1.25]





Footnotes
(1) After 6 months' treatment

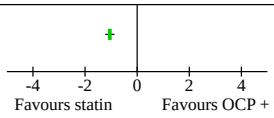
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. Statin versus oral contraceptive pill (OCP) plus flutamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Body mass index (kg/m^2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2 Waist circumference (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3 High-density lipoprotein (HDL) cholesterol (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4 Triglycerides (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 High-sensitivity C-reactive protein (nmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Statin versus oral contraceptive pill (OCP) plus flutamide, Outcome 1: Body mass index (kg/m^2)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	OCP + flutamide Mean	OCP + flutamide SD	OCP + flutamide Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Mehrabian 2016 (1)	-1.13	0.391	34	-0.08	0.345	34	-1.05 [-1.23 , -0.87]		?	?	?	−	−	?

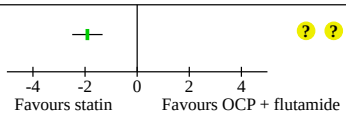


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 5.2. Comparison 5: Statin versus oral contraceptive pill (OCP) plus flutamide, Outcome 2: Waist circumference (cm)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	OCP + flutamide Mean	OCP + flutamide SD	OCP + flutamide Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mehrabian 2016 (1)	-2.79	1.61	34	-0.88	0.64	34	-1.91 [-2.49 , -1.33]		? ? ? − − ?

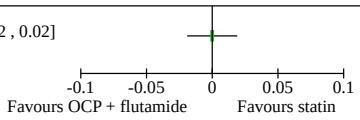


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 5.3. Comparison 5: Statin versus oral contraceptive pill (OCP) plus flutamide, Outcome 3: High-density lipoprotein (HDL) cholesterol (mmol/L)

Study or Subgroup	Statin Mean	Statin SD	Statin Total	OCP + flutamide Mean	OCP + flutamide SD	OCP + flutamide Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mehrabian 2016 (1)	-0.01	0.04	34	-0.01	0.04	34	0.00 [-0.02 , 0.02]		? ? ? − − ?

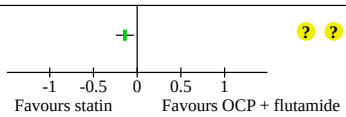


Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 5.4. Comparison 5: Statin versus oral contraceptive pill (OCP) plus flutamide, Outcome 4: Triglycerides (mmol/L)

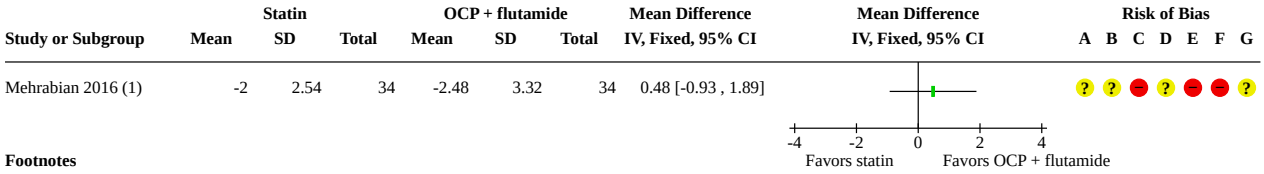
Study or Subgroup	Statin Mean	Statin SD	Statin Total	OCP + flutamide Mean	OCP + flutamide SD	OCP + flutamide Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mehrabian 2016 (1)	-0.28	0.3	34	-0.14	0.05	34	-0.14 [-0.24 , -0.04]		? ? ? − − ?



Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 5.5. Comparison 5: Statin versus oral contraceptive pill (OCP) plus flutamide, Outcome 5: High-sensitivity C-reactive protein (nmol/L)



Footnotes
(1) After 6 months' treatment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Conversion factors

	Convert from	Convert to	Conversion factor
Cholesterol	mg/dL	mmol/L	0.026
Triglycerides	mg/dL	mmol/L	0.011
Insulin	pmol/L	µIU/L	0.1667
Glucose	mg/dL	mmol/L	0.056
Testosterone	ng/dL	nmol/L	0.03467
High-sensitivity C-reactive protein	mg/L	nmol/L	9.524
Standard deviation	Standard error	Standard deviation	Sqrt n
Confidence intervals	Confidence intervals	Standard error	(upper limit−lower limit)/3.92

Table 2. Baseline characteristics of included studies

Study ID	Study group (n)	Baseline demographics, mean (SD)		Baseline biochemistry, mean (SD)					
		Age (years)	BMI (kg/m²)	Total T (nmol/L)	FI (µIU/ml)	TC (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	TG (mmol/L)
Banaszewska 2011[a]	I1: sim + met (44)	25.3 (4.0)	24.8 (5.3)	2.95 (0.92)	8.10 (5.31)	4.79 (0.83)	1.68 (0.38)	2.64 (0.76)	1.02 (0.58)
	I2: sim (48)	26.3 (4.2)	23.5 (4.2)	2.91 (0.72)	6.90 (4.90)	4.96 (0.97)	1.79 (0.40)	2.80 (0.88)	0.79 (0.24)
	C: met (47)	26.0 (4.1)	24.7 (4.8)	2.91 (0.95)	8.10 (4.11)	4.53 (0.73)	1.57 (0.39)	2.51 (0.75)	0.87 (0.51)
Duleba 2006[b]	I: sim + OCP (24)	24.0 (3.4)	21.7 (2.5)	2.96 (0.82)	8.1 (3.92)	5.02 (0.76)	1.69 (0.51)	2.78 (0.64)	0.97 (0.43)
	C: OCP (24)	23.8 (3.9)	22.8 (3.9)	2.62 (0.87)	8.9 (4.41)	4.86 (1.15)	1.59 (0.25)	2.76 (0.76)	1.08 (0.48)
Mehrabian 2016	I: sim (34)	29.2 (8.3)	29.9 (4.1)	NR	NR	NR	1.10 (0.18)	NR	2.21 (0.59)
	C1: OCP + flu (34)	29.0 (7.7)	29.8 (4.2)				1.11 (0.18)		2.20 (0.58)
	C2: met (34)	29.2 (8.3)	29.8 (4.1)				1.11 (0.19)		2.20 (0.59)
Puurunen 2013	I: AT (15)	40.5 (5.9)	30.4 (8.6)	1.4 (0.80)	13.30 (10.30)	5.20 (0.80)	1.52 (0.40)	3.30 (0.80)	1.20 (0.50)
	C: P (13)	38.5 (4.8)	26.7 (4.7)	0.9 (0.30)	7.10 (3.60)	4.90 (0.90)	1.50 (0.30)	3.00 (1.00)	1.00 (0.40)
Raja-Khan 2011	I: AT (9)	33.8 (4.3)	40.1 (11.8)	2.13 (0.59)	18.6 (10.10)	5.58 (1.00)	1.15 (0.38)	3.64 (0.64)	1.73 (0.93)
	C: P (11)	29.4 (5.8)	36.0 (10.4)	3.20 (1.73)	16.8 (9.50)	5.24 (0.74)	1.20 (0.22)	3.40 (0.56)	1.41 (0.60)
Sathyapalan 2009	I: AT (19)	26.6 (5.2)	33.2 (6.1)	4.10 (0.87)	15.6 (7.85)	4.60 (0.87)	1.07 (0.44)	2.90 (0.87)	1.34 (0.35)
	C: P (18)	28.8 (7.6)	33.9 (5.9)	4.40 (0.85)	14.4 (8.49)	4.50 (0.85)	1.10 (0.34)	2.70 (0.85)	1.39 (1.02)

a. 86% of participants had irregular menstrual cycle (≤ 8 spontaneous cycles/year), 79% had hirsutism, and 82% had acne.
b. 73% of participants had irregular menstrual cycle.
AT: atorvastatin; BMI: body mass index; C: control; I: intervention; FI: fasting insulin; flu: flutamide; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; met: metformin; NR: not reported; sim: simvastatin; SD: standard deviation; T: testosterone; TC: total cholesterol; TG: total glucose.

Table 3. Attrition table

Study ID	Screened, n	Treatment groups	Randomised, n	Completed, n (%)	Reasons for attrition
Banaszewska 2011	150	I1: simvastatin + metformin	44	3 months: 37 (84%) 6 months: 36 (82%)	Loss of contact due to changes in telephone, mail, or residence address; or immigration
		I2: simvastatin	48	3 months: 41 (85%) 6 months: 28 (58%)	
		C: metformin	47	3 months: 36 (77%) 6 months: 33 (70%)	
		All participants	139	3 months: 114 (82%) 6 months: 97 (70%)	
Duleba 2006	54	I: simvastatin + OCP	24	24 (100%)	NA
		C: OCP	24	24 (100%)	
		All participants	48	48 (100%)	
Mehrabian 2016	NR	I: simvastatin	37	34 (92%)	Loss to follow-up, non-compliance with study protocol, refusal to continue participating in study, not using allocated treatment
		C1: flutamide + OCP	37	34 (92%)	
		C2: metformin	37	34 (92%)	
		All participants	111	102 (92%)	
Puurunen 2013	NR	I: atorvastatin	20	15 (75%)	T2DM (n = 1), non-adherence (n = 2), arthralgia (n = 1)
		C: placebo	19	13 (68%)	Menorrhagia with anaemia (n = 1), T2DM (n = 2), non-adherence (n = 2), myalgia (n = 1)
		All participants	39	28 (72%)	—
Raja-Khan 2011	NR	I: atorvastatin	9	NR	Use of OCP during follow-up period
		C: placebo	11	NR	
		All participants	20	18 (90%)	
Sathyapalan 2009	40/40	I: atorvastatin	20	19 (95%)	Non-compliance with statins regimen based on pill count
		C: placebo	20	18 (90%)	
		All participants	40	37(93%)	
Total			1345	1295 (96.3%)	—

C: control; I: intervention; NA: not applicable; NR: not reported; OCP: oral contraceptive pill; T2DM: type 2 diabetes mellitus.

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register (CGF) search strategy

Searched from inception until 7 November 2022

ProCite platform

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 "statins" or "lovastatin" or "pravastatin" or "simvastatin" or "atorvastatin" or "rosuvastatin calcium" or Title CONTAINS "statins" or "lovastatin" or "pravastatin" or "simvastatin" or "atorvastatin" or "rosuvastatin calcium"

(35 records)

Appendix 2. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

Searched from inception until 7 November 2022

CRSO Web platform

#1 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES 1689

#2 (Polycystic Ovar*):TI,AB,KY 4184

#3 PCO*:TI,AB,KY 5566

#4 (stein-leventhal or leventhal):TI,AB,KY 69

#5 Hyperandrog*:TI,AB,KY 822

#6 #1 OR #2 OR #3 OR #4 OR #5 6830

#7 MESH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors EXPLODE ALL TREES 6707

#8 MESH DESCRIPTOR Lovastatin EXPLODE ALL TREES 2209

#9 MESH DESCRIPTOR Meglutol EXPLODE ALL TREES 2

#10 MESH DESCRIPTOR Pravastatin EXPLODE ALL TREES 1018

#11 MESH DESCRIPTOR Simvastatin EXPLODE ALL TREES 1837

#12 (HMG coenzyme reductase):TI,AB,KY 1

#13 statin:TI,AB,KY or statins:TI,AB,KY 9604

#14 (Atorvastatin or Simvastatin):TI,AB,KY 8601

#15 (Rosuvastatin or Lovastatin):TI,AB,KY 3491

#16 (Mevastatin or Pravastatin):TI,AB,KY 1934

#17 mevinolin:TI,AB,KY 104

#18 (HMG-coA reductase*):TI,AB,KY 985

#19 (HMG coenzyme A reductase):TI,AB,KY 25

#20 Zocor:TI,AB,KY 86

#21 meglutol:TI,AB,KY 2

#22 (Hydroxymethylglutaryl CoA Reductase):TI,AB,KY 3751

#23 (Hydroxy 3 methylglutaryl CoA Reductase):TI,AB,KY 16

#24 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 17418

#25 #6 AND #24 74

Appendix 3. MEDLINE search strategy

Searched from 1946 until 7 November 2022

Ovid platform

1 exp Polycystic Ovary Syndrome/ (17175)
2 Polycystic Ovar$.tw. (20070)
3 PCO$.tw. (36238)
4 (stein-leventhal or leventhal).tw. (737)
5 (ovar$ adj1 sclerocystic).tw. (104)
6 Hyperandrog$.tw. (6041)
7 (ovar$ adj1 degeneration).tw. (57)
8 or/1-7 (46668)
9 exp hydroxymethylglutaryl-coa reductase inhibitors/ or exp lovastatin/ or exp meglutol/ or exp pravastatin/ or exp simvastatin/ (45606)
10 HMG coenzyme reductase.tw. (1)
11 $statin$.tw. (49450)
12 (Atorvastatin or Simvastatin).tw. (18102)
13 (Rosuvastatin or Lovastatin).tw. (7782)
14 (Mevastatin or Pravastatin).tw. (4470)
15 mevinolin.tw. (402)
16 HMG-coA reductase$.tw. (8053)
17 HMG coenzyme A reductase.tw. (70)
18 Zocor.tw. (115)
19 meglutol.tw. (3)
20 Hydroxymethylglutaryl CoA Reductase.tw. (347)
21 Hydroxy 3 methylglutaryl CoA Reductase.tw. (1224)
22 CoA Reductase, 3-Hydroxy-3-methylglutaryl.tw. (4)
23 Reductase, 3-Hydroxy-3-methylglutaryl CoA.tw. (6)
24 or/9-23 (76474)
25 8 and 24 (171)
26 randomized controlled trial.pt. (579933)
27 controlled clinical trial.pt. (95083)
28 randomized.ab. (580907)
29 placebo.tw. (239192)
30 clinical trials as topic.sh. (200534)
31 randomly.ab. (394524)
32 trial.ti. (272969)
33 (crossover or cross-over or cross over).tw. (95490)
34 or/26-33 (1517581)
35 (animals not (humans and animals)).sh. (5026997)
36 34 not 35 (1394947)
37 25 and 36 (50)

Appendix 4. Embase search strategy

Searched from 1980 until 7 November 2022

Ovid platform

1 exp ovary polycystic disease/ (32842)
2 Polycystic Ovar$.tw. (28064)
3 PCO$.tw. (48991)
4 (stein-leventhal or leventhal).tw. (332)
5 (ovar$ adj1 sclerocystic).tw. (47)
6 (ovar$ adj2 degeneration).tw. (156)
7 Hyperandrog$.tw. (8797)
8 or/1-7 (66878)

9 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ (180794)
10 HMG coenzyme reductase.tw. (3)
11 hydroxymethylglutaryl-coa reductase inhibitor$.tw. (117)
12 $statin$.tw. (81454)
13 (Atorvastatin or Simvastatin).tw. (29317)
14 (Rosuvastatin or Lovastatin).tw. (12082)
15 (Mevastatin or Pravastatin).tw. (6376)
16 mevinolin.tw. (492)
17 HMG-coA reductase$.tw. (10525)
18 HMG coenzyme A reductase.tw. (88)
19 Zocor.tw. (2007)
20 meglutol.tw. (4)
21 Hydroxymethylglutaryl CoA Reductase.tw. (331)
22 Hydroxy 3 methylglutaryl CoA Reductase.tw. (1244)
23 CoA Reductase, 3-Hydroxy-3-methylglutaryl.tw. (7)
24 Reductase, 3-Hydroxy-3-methylglutaryl CoA.tw. (8)
25 or/9-24 (204289)
26 Clinical Trial/ (1037452)
27 Randomized Controlled Trial/ (730432)
28 exp randomization/ (95496)
29 Single Blind Procedure/ (48044)
30 Double Blind Procedure/ (197211)
31 Crossover Procedure/ (71816)
32 Placebo/ (373359)
33 Randomi?ed controlled trial$.tw. (298667)
34 Rct.tw. (49169)
35 random allocation.tw. (2390)
36 randomly allocated.tw. (42528)
37 allocated randomly.tw. (2821)
38 (allocated adj2 random).tw. (851)
39 Single blind$.tw. (29460)
40 Double blind$.tw. (227821)
41 ((treble or triple) adj blind$).tw. (1656)
42 placebo$.tw. (344655)
43 prospective study/ (804799)
44 or/26-43 (2594247)
45 case study/ (89333)
46 case report.tw. (492600)
47 abstract report/ or letter/ (1209436)
48 or/45-47 (1777619)
49 44 not 48 (2532460)
50 8 and 25 and 49 (185)

Appendix 5. PsycINFO search strategy

Searched from 1806 until 7 November 2022

Ovid platform

1 exp endocrine sexual disorders/ (1780)
2 Polycystic Ovar$.tw. (514)
3 PCO$.tw. (1127)
4 (stein-leventhal or leventhal).tw. (321)
5 (ovar$ adj1 sclerocystic).tw. (1)
6 (ovar$ adj1 degeneration).tw. (0)
7 Hyperandrog$.tw. (163)
8 or/1-7 (3228)
9 exp statins/ (790)
10 HMG coenzyme reductase.tw. (0)
11 hydroxymethylglutaryl-coa reductase inhibitor$.tw. (8)
12 statin$.tw. (5733)
13 (Atorvastatin or Simvastatin).tw. (501)
14 (Rosuvastatin or Lovastatin).tw. (151)

15 (Mevastatin or Pravastatin).tw. (102)
16 mevinolin.tw. (0)
17 HMG-coA reductase$.tw. (143)
18 HMG coenzyme A reductase.tw. (1)
19 Zocor.tw. (5)
20 meglutol.tw. (0)
21 Hydroxymethylglutaryl CoA Reductase.tw. (9)
22 Hydroxy 3 methylglutaryl CoA Reductase.tw. (13)
23 CoA Reductase, 3-Hydroxy-3-methylglutaryl.tw. (0)
24 Reductase, 3-Hydroxy-3-methylglutaryl CoA.tw. (0)
25 or/9-24 (6165)
26 8 and 25 (4)

Appendix 6. CINAHL search strategy

Searched from 1961 to 25 September 2019 (All CINAHL trials from 25 September 2019 to 7 Novemeber 2022 are included in the CENTRAL 2022 search output)

Ovid platform

#	Query	Results
S18	S7 AND S17	43
S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	21,356
S16	TX Zocor	41
S15	TX HMG-coA reductase	749
S14	TX mevinolin	2
S13	TX (Mevastatin or Pravastatin)	1,029
S12	TX (Rosuvastatin or Lovastatin)	1,638
S11	TX (Atorvastatin or Simvastatin)	4,477
S10	TX statin*	17,558
S9	TX HMG coenzyme reductase	144
S8	(MM "Statins+") OR (MM "Simvastatin") OR (MM "Rosuvastatin") OR (MM "Pravastatin") OR (MH "Pitavastatin Calcium") OR (MH "Fluvastatin") OR (MH "Amlodipine Besylate Atorvastatin Calcium")	6,571
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	7,786
S6	TX ovar* N1 degeneration	7
S5	TX Hyperandrog*	809
S4	TX (stein-leventhal or leventhal)	1,044
S3	TX PCO*	4,374
S2	TX Polycystic Ovar*	4,117

(Continued)

S1	(MM "Polycystic Ovary Syndrome")	2,587

WHAT'S NEW

Date	Event	Description
18 July 2023	New search has been performed	Two new studies added: Mehrabian 2016; Puurunen 2013
18 July 2023	New citation required and conclusions have changed	Change in conclusion on effect of statins in reducing serum total testosterone levels.

HISTORY

Protocol first published: Issue 7, 2010
Review first published: Issue 10, 2011

Date	Event	Description
19 April 2010	Amended	Title has been modified. Previously title was 'Statin for polycystic ovary syndrome'.

CONTRIBUTIONS OF AUTHORS

TX screened and selected studies, extracted data, assessed risk of bias and certainty of the evidence, assessed data integrity of the studies, and wrote the review.
EF screened and selected studies, extracted data, assessed risk of bias and certainty of the evidence, assessed data integrity of the studies, and approved the final draft for publication.
EK screened studies, extracted data, assessed risk of bias and certainty of evidence, assessed data integrity of the studies, and approved the final draft for publication.
MFC provided consultation on the screening and selection of studies, extraction of data, and data analysis; revised the review critically for important intellectual content; and approved the final draft for publication.
CV provided consultation on the screening and selection of studies, extraction of data, and data analysis; revised the review critically for important intellectual content; and approved the final draft for publication.
EBK screened studies, discussed discrepancies in certainty of the evidence and risk of bias with the other review authors, checked extracted data, assessed data integrity of the studies, and wrote the review.

DECLARATIONS OF INTEREST

TX has no conflicts of interest to declare.
EF has no conflicts of interest to declare.
EK has no conflicts of interest to declare.
MFC declares past sponsorship from Merck for scientific conference presentations.
CV declares honoraria, fees or travel sponsorship by Merck, Merck Sharp & Dohme, Organon, Ferring, Gedeon-Richter and Besins.
EBK is a Managing Editor of the Cochrane Gynaecology and Fertility Group and confirms that she was not involved in the editorial process for this update. EBK has no other conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- None, Other

  None

External sources

- None, Other

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Raval 2010 (review protocol).

There are minor changes in the introduction of the review.

We had planned sensitivity analyses including only trials with low risk of selection bias (random sequence generation and allocation concealment) for all primary outcomes. We assessed the certainty of the evidence using GRADE and added summary of findings tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Atorvastatin; Heptanoic Acids [therapeutic use]; Hirsutism [drug therapy]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*therapeutic use]; Hyperandrogenism [drug therapy]; Hypoglycemic Agents [therapeutic use]; Menstruation Disturbances [drug therapy]; Metformin [therapeutic use]; Polycystic Ovary Syndrome [blood] [*drug therapy]; Pyrroles [therapeutic use]; Randomized Controlled Trials as Topic; Simvastatin [therapeutic use]

MeSH check words

Adult; Female; Humans; Young Adult