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# Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history (Review)

Chen H, Fu J, Huang W

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[Intervention Review]

# Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history

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## ABSTRACT

### Background

Hyperprolactinemia is the presence of abnormally high circulating levels of prolactin. Idopathic hyperprolactinemia is the term used when no cause of prolactin hypersecretion can be identified and it is causally related to the development of miscarriage in pregnant women, especially women who have a history of recurrent miscarriage. A possible mechanism is that high levels of prolactin affect the function of the ovaries, resulting in a luteal phase defect and miscarriage. A dopamine agonist is a compound with high efficacy in lowering prolactin levels and restoring gonadal function.

### Objectives

To assess the effectiveness and safety of different types of dopamine agonists in preventing future miscarriage given to women with idiopathic hyperprolactinemia and a history of recurrent miscarriage.

### Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2016) and reference lists of retrieved studies.

### Selection criteria

Randomized controlled trials (RCTs) in all languages examining the effect of dopamine agonists on preventing future miscarriage. Women who had idiopathic hyperprolactinemia with a history of recurrent miscarriages were eligible for inclusion in this review. Comparisons planned included: dopamine agonists alone versus placebo/no treatment; and dopamine agonists combined with other therapy versus other therapy alone.

### Data collection and analysis

Two review authors independently assessed a single trial for inclusion, evaluated trial quality and extracted data. Data were checked for accuracy.

### Main results

One study (recruiting 48 women with idiopathic hyperprolactinemia) met our inclusion criteria; 46 women (42 pregnancies - 4/46 women did not conceive during the study period) were included in the analysis. The study compared the use of a dopamine agonist (bromocriptine, 2.5 mg to 5.0 mg/day until the end of the ninth week of gestation) versus a no-treatment control. The study was judged as being at a high risk of bias. It was not possible to carry out meta-analysis due to insufficient data.

The study reported both of this review's primary outcomes of miscarriage and live birth. Results from this single study suggest that, compared to no treatment, oral bromocriptine was effective in preventing future **miscarriage** (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.09 to 0.87, 46 participants (*low-quality evidence*)) in women with idiopathic hyperprolactinemia. There was no clear difference with regard to the other primary outcome of **live births** (RR 1.50, 95% CI 0.93 to 2.42, 46 participants (*very low-quality evidence*)).

There was no difference with regard to this review's secondary outcome of **conception** (RR 0.92, 95% CI 0.77 to 1.09, 46 participants (*very low-quality evidence*)) between the group of women who received dopamine (21 out of 24 women conceived) and women in the no-treatment group (21 out of 22 women conceived). The included study only reported the **serum prolactin levels** in pregnant women and therefore the data could not be analyzed in this review. No other secondary outcomes relevant to this review were reported; adverse effects for women (nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms) and infants (birth defects, low birthweight, and developmental disabilities) were not reported.

We downgraded the quality of the evidence for risk of bias in the one trial contributing outcome data (no description of allocation concealment, lack of blinding and possible reporting bias) and for imprecision (all effect estimates were based on small sample size, miscarriage was based on few events, and the 95% CIs of live birth and conception cross the line of no effect).

### Authors' conclusions

Currently, there is insufficient evidence (from a single randomized trial with a small sample size, and judged to be at high risk of bias) to evaluate the effectiveness of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. We assessed outcomes using GRADE methodology. Miscarriage was assessed as low quality due to risk of bias concerns in the one trial contributing data (no description of allocation concealment, lack of blinding and possible reporting bias) and to imprecision (effect estimates were based on small sample size and few events). Live births and conception were assessed as of very low quality due to the same risk of bias concerns in study design and to imprecision (with a wide 95% CI consistent with either benefit or harm), and a small sample size. There were no data relating to adverse effects of the intervention for either the mother or her baby.

Futher high-quality research in this area is warranted. There is a need for well-designed, larger RCTs to confirm and extend the findings of the trial reviewed here. Many questions remain unanswered. Some important considerations for future research include, the need for well-designed RCTs with large sample sizes, and for those studies to consider important outcomes (including adverse effects for both the mother and her baby). Future studies should examine the effectiveness and safety of various dopamine agonists including bromocriptine, cabergoline and quinagolide.

## PLAIN LANGUAGE SUMMARY

### Dopamine agonists for preventing future miscarriage in women with high prolactin levels and a history of recurrent miscarriage

#### What is the issue

Hyperprolactinemia is the presence of high circulating serum levels of prolactin, a hormone that is best known for its role in lactation. Idopathic hyperprolactinemia is the term used when no cause of prolactin hypersecretion can be identified and it is associated with miscarriage in pregnant women, especially women who have experienced several unexplained pregnancy losses. Occult hyperprolactinemia where prolactin levels are normal in the morning but rise during the day is one special type of hyperprolactinemia that is also associated with miscarriage. A dopamine agonist is a type of drug that is highly effective in lowering prolactin levels. One such drug is bromocriptine. It restores important functions of the ovaries that could allow women to maintain pregnancy.

#### Why is this important

We were most interested to know if dopamine agonists could lower rates of miscarriage and improve women's chances of having a live birth. We reviewed the evidence about the effectiveness and safety of dopamine agonists for preventing future miscarriage in women with a history of recurrent miscarriage.

#### What evidence did we find

We searched for evidence on 30 June 2016 and identified one trial with a small number of women - 48 women were recruited but 46 women (42 pregnancies - 4/46 women did not conceive during the study period) are included in the analysis). The trial took place in Japan and was judged to have a high risk of bias. The trial included women (aged 24 to 40 years) with idiopathic hyperprolactinemia and a history of two to four spontaneous miscarriages; 24 had occult hyperprolactinemia with equal numbers in each group. Women were followed during the study (until the end of the ninth week of pregnancy) and then observed for one year afterwards. In the study, one group of women received a dopamine agonist, bromocriptine (2.5 to 5.0 mg/day until the end of the ninth week of gestation), and the other group of women did not receive any treatment (control group).

Evidence from this study showed that the dopamine agonist bromocriptine was effective in preventing future miscarriage (*low-quality evidence*). However, live birth and conception rates remained similar between women who received bromocriptine and the women who did not receive treatment (*very low-quality evidence*). The study only reported on serum prolactin levels in the women who were pregnant. The study did not report on any adverse effects that dopamine agonists might possibly have for the women (e.g. nausea, vomiting, headache,

vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms) or her baby (e.g. birth defects, low birthweight, and developmental disabilities).

**What does this mean**

We rated the evidence for the review outcomes of miscarriage as low quality and live birth and conception as very low quality due to questions we had about the study design, the small number of women in the study, and because only one randomized controlled study was identified. Currently, there is not enough evidence (from one small trial) to evaluate the effectiveness and safety of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. There is a need for further, high-quality research in this area. Future studies (involving large numbers of women) are needed to expand on the findings of this review. Further studies should examine various dopamine agonists (including bromocriptine, cabergoline and quinagolide) and consider important outcomes (including adverse effects for both the mother and her baby).

**Summary of findings for the main comparison. Bromocriptine versus no treatment for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history**

**Bromocriptine treatment versus no treatment for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history**

**Patient or population:** women with idiopathic hyperprolactinemia and recurrent miscarriage history
**Settings:** recurrent spontaneous abortion clinic, Yokohama City University Hospital, Japan
**Intervention:** dopamine agonists (bromocriptine) alone

**Comparison**: no treatment

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo/no treatment | Risk with Dopamine agonists alone | | | | |
| **Miscarriages** | **Study population** | | **RR 0.28** (0.09 to 0.87) | 46 (1 study) | ⊕⊕⊖⊖ **low** [1,2] | |
| | **455 per 1000** | **127 per 1000** (41 to 395) | | | | |
| | **Moderate** | | | | | |
| | **455 per 1000** | **127 per 1000** (41 to 396) | | | | |
| **Live births** | **Study population** | | **RR 1.50** (0.93 to 2.42) | 46 (1 study) | ⊕⊖⊖⊖ **very low** [1,3,4] | |
| | **500 per 1000** | **750 per 1000** (465 to 1000) | | | | |
| | **Moderate** | | | | | |
| | **500 per 1000** | **750 per 1000** (465 to 1000) | | | | |
| **Conception** | **Study population** | | **RR 0.92** (0.77 to 1.09) | 46 (1 study) | ⊕⊖⊖⊖ **very low** [1,3,4] | |
| | **955 per 1000** | **878 per 1000** (735 to 1000) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **Moderate** | | | | | |
| | **955 per 1000** | **878 per 1000** (735 to 1000) | | | | |
| **Proportion reduction in serum prolactin levels** | **Study population** | | Not estimable | 0 (0) | See comment | No data in included study |
| | See comment | See comment | | | | |
| | **Moderate** | | | | | |
| | | | | | | |
| **Serum prolactin normalization** | **Study population** | | Not estimable | 0 (0) | See comment | No data in included study |
| | See comment | See comment | | | | |
| | **Moderate** | | | | | |
| | | | | | | |
| **Adverse maternal effects** | **Study population** | | Not estimable | 0 (0) | See comment | No data in included study |
| | See comment | See comment | | | | |
| | **Moderate** | | | | | |
| | | | | | | |
| **Adverse fetal outcomes** | **Study population** | | Not estimable | 0 (0) | See comment | No data in included study |
| | See comment | See comment | | | | |
| | **Moderate** | | | | | |
| | | | | | | |

*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; **RR:** Risk ratio.

GRADE Working Group grades of evidence

**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** 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 quality:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] One trial with design limitations, including no description of allocation concealment, lack of blinding and possible outcome reporting bias (-1).
[2] Estimate based on small sample size and few events (-1).
[3] Estimate based on small sample size (-1).
[4] 95% CI overlap with non-significant line with small sample size (-1).

# BACKGROUND

## Description of the condition

### Recurrent miscarriage

Recurrent miscarriage is defined as three or more consecutive spontaneous abortions at a stage where the embryo or fetus is incapable of surviving, generally within the first 20 weeks of gestation (Dlugi 1998; Katharina 2008). With the declining birth trend, more and more researchers tend to define recurrent miscarriage to be at least two spontaneous abortions (Toth 2010). Ten per cent to 15% of all clinically recognized pregnancies end in a miscarriage (Regan 1989), and recurrent miscarriage affects 1% to 3% of all women (Stirrat 1990; Toth 2010). The most common symptoms of a miscarriage are vaginal bleeding and lower abdominal pain (Yip 2003).

Recurrent miscarriage is a heterogeneous condition, of which the etiology is not completely understood. Known risk factors include chromosomal abnormalities, endocrine disorders (luteal phase deficiency, thyroid disorders, diabetes mellitus, high androgen levels, hyperprolactinemia, polycystic ovary syndrome, antiphospholipid syndrome, et al), anatomic abnormalities (uterine synechiae, cervical incompetence, intrauterine adhesion, uterine malformation such as uterine septum, uterine fibroids, scar tissue, et al), immunologic factors (humoral response abnormalities, cellular response abnormalities, et al), infections and endometriosis (Dlugi 1998; García-Enguídanos 2002; Daya 2004; Toth 2010). Increased age, smoking, caffeine or alcohol intake, and administration of certain drugs may also increase the incidence of miscarriage (García-Enguídanos 2002). However, nearly 50% of recurrent miscarriages are unexplained (Toth 2010).

### Hyperprolactinemia

#### *Biological action of prolactin*

Prolactin was first confirmed in humans in 1970 (Friesen 1970). It is a 23 kDa polypeptide hormone (198 amino acid) with a structure similar to that of growth hormone and placental lactogen (Mancini 2008; Majumdar 2013). It is mainly produced by the lactotrope cells in the anterior pituitary gland with a diurnal secretion pattern, peaking during rapid eye movement in the early morning, and decreasing thereafter. In normal conditions, its secretion is regulated by the prolactin inhibitory factors (PIF) and prolactin-releasing factors (PRF) from the pituitary. Dopamine, the main PIF, acts on surface membrane dopamine $D_2$ receptors on lactotroph cells to decrease prolactin. Physical factors (stress, food ingestion, pregnancy, trauma, et al) or pathological factors (some drugs, pituitary tumors, systemic and endocrine diseases, et al) could affect serum prolactin levels (Majumdar 2013). The actual serum prolactin level is the result of a balance between various internal and external, positive and negative factors. With commonly used assays, normal serum prolactin levels vary from 5 µg/L to 25 µg/L in women (Melmed 2008).

Prolactin is best known for its role in inducing and maintaining lactation; in addition, it exerts metabolic effects, regulates functions of lymphocytes and stimulates immune responsiveness, takes part in reproductive mammary development, participates in osmoregulation, provides the body with sexual gratification after sex, and contributes to surfactant synthesis of the fetal lungs (Tyson 1973; Majumdar 2013).

#### *Definition and etiology*

Hyperprolactinemia is the presence of abnormally high circulating levels of prolactin, which is usually defined to be above 25 µg/L (530 mIU/L (milli-international units per liter)) in women (Chahal 2008; Melmed 2011). Known reasons include physiological hypersecretion (pregnancy, breastfeeding, stress, et al), drug-induced hypersecretion (dopamine receptor blockers, dopamine synthesis inhibitors, calcium channel blockers, et al), pituitary hypersecretion (prolactinomas, et al), systemic and endocrine diseases (renal failure, hepatic failure, primary hypothyroidism, polycystic ovary syndrome (PCOS), et al) (Stirrat 1990; Chahal 2008; Glezer 2014).

When no cause of hyperprolactinemia can be identified, the condition is termed idiopathic hyperprolactinemia (Majumdar 2013). Long-term follow-up found that microadenomas show up in approximately 10% of those patients that were too small to be detected originally (Chahal 2008). Occult hyperprolactinemia (or latent hyperprolactinemia) is one special type of idiopathic hyperprolactinemia in which the serum prolactin levels are normal in the morning, but become excessive during the day, or under stimulation (Schenker 1992; Kostál 1997). This condition could be detected by thyrotropin-releasing hormone (TRH) test or metoclopramide test (MCT) (Aisaka 1993; Kostál 1997). Some researchers have defined occult hyperprolactinemia as a prolactin level above 70 µg/L at 30 minutes after TRH injection (Aisaka 1993). Others have defined it as prolactin level above 150 ng/mL at 30 minutes after metoclopramide administration (Schenker 1992; Kostál 1997). However, the criteria for hyperprolactinemia, including occult hyperprolactinemia, may vary among different laboratories and different groups of people.

#### *Prevalence*

Hyperprolactinemia is a common endocrine disorder in women. The prevalence was found to be 0.4% in an unselected population, 5% in a family planning clinic, 9% in women with adult onset amenorrhea, 17% among women with PCOS (Majumdar 2013), and 36% among recurrent miscarriage patients (Hirahara 1996; Bussen 1999). Idiopathic hyperprolactinemia accounts for 40% of hyperprolactinemia (Huang 2007). Occlut hyperprolactinemia was claimed to cause 43% to 70% of luteal phase disorders (Mühlenstedt 1977; Aisaka 1993), and was observed at night in 80% of patients with normal prolactin levels who had galactorrhea (Aisaka 1993).

#### *Clinical manifestations*

A high serum prolactin level does not just inhibit the secretion of follicle-stimulating hormone (FSH) and gonadotropin-releasing hormone (GnRH), but it directly inhibits the secretion of estradiol and progesterone, leading to hypogonadism and hypoestrogenemia. Clinical manifestations of hyperprolactinemia include galactorrhea, menses changes (menstrual flow changes, irregular menses, amenorrhea, et al), reproductive dysfunction (anovulation, luteal insufficiency, miscarriage, et al), a long-term risk of osteopenia, and loss of interest in sex (Ben-David 1983; Yamaguchi 1991; Asukai 1993; Hirahara 1998; Majumdar 2013; Molitch 2015).

Clinical observations have found prolactin concentrations were significantly higher in women experiencing recurrent miscarriage, suggesting that hyperprolactinemia was causally related to

the development of miscarriage, especially in women with recurrent miscarriage in whom no other cause for their repeated pregnancy loss was apparent (Ando 1992; Hirahara 1996; Hirahara 1998; Bussen 1999). Hirahara identified this situation as hyperprolactinemic recurrent miscarriage (Hirahara 1998). A possible mechanism is that high levels of prolactin affect the function of the ovaries, resulting in a luteal phase defect and miscarriage.

#### *Diagnosis*

A serum prolactin above normal (usually 25 µg/L) confirms the diagnosis of hyperprolactinemia (Chahal 2008; Melmed 2011). It should be measured in the morning at least two hours after waking up to ensure the measurement is accurate. Other factors affecting the result include non-fasting sample, excessive exercise and history of drug intake (Majumdar 2013). The diagnosis should be cautious when the prolactin level is slightly elevated and the examination should be repeated later. A falsely-high measurement may occur due to the presence of the biologically-inactive macroprolactin in the serum. This can show up as high prolactin in some types of tests, but is asymptomatic. The TRH stimulation test is used as a provocative pituitary test, which is helpful to detect patients with normal baseline serum prolactin levels and a greater capacity for prolactin secretion after TRH administration (Dlugi 1998).

Medical history is collected to exclude possible etiology. Patients should be evaluated for symptoms including amenorrhea or oligomenorrhea, infertility, fractures, vision changes, and galactorrhea et al. Magnetic resonance imaging (MRI) is the most sensitive test for detecting pituitary tumors and computed tomography (CT) is the second choice.

### Description of the intervention

A dopamine agonist is a compound that activates signaling pathways through the dopamine receptor in the brain. Its high efficacy has been well-demonstrated in lowering prolactin levels, reducing prolactinoma size, and restoring gonadal function (Webster 1999; Gillam 2006; Melmed 2011). A systematic review found the proportions of patients with hyperprolactinemia with improved outcomes under dopamine agonists are: normalization of prolactin level (68%; 40% to 100%), reduction in tumor size (mean 62%; range 20% to 100%), resolution of amenorrhea (78%; 40% to 100%), resolution of infertility (53%; 10% to 100%), resolution of galactorrhea (86%; 33% to 100%), and improvement of sexual function (67%; 6% to 100%) (Wang 2012). Ovulation rates achieved by dopamine agonist treatment only are approximately 80% to 90% if hyperprolactinemia is the only cause for anovulation (Majumdar 2013). Sixty per cent of patients with galactorrhea and 47% of patients with luteal insufficiency with occult hyperprolactinemia recovered after bromocriptine treatment (Aisaka 1993). Side effects mainly include nausea, vomiting, headache, hypotension, arrhythmia, and psychotic symptoms. The most commonly used dopamine agonists for hyperprolactinemia are bromocriptine, cabergoline and quinagolide. Others include lisuride, pergolide, quinagolide, terguride, and metergoline et al. Although it is generally recommended to withdraw dopamine agonist therapy during pregnancy in patients with prolactinomas, there is evidence about the safety of some kind of dopamine agonists (mainly bromocriptine, cabergoline and quinagolide) use during pregnancy.

Bromocriptine is the first option for hyperprolactinemia. It is a lysergic acid derivative with a bromine substitute at position 2 (Vance 1984), and acts as a strong dopamine agonist. It decreases DNA synthesis, prolactin synthesis, and cell multiplication. Bromocriptine is initiated at 1.25 mg to 2.5 mg in divided doses administered twice a day. The majority of patients with hyperprolactinemia respond to bromocriptine in doses of 7.5 mg/day (Morange 1996). Some patients are intolerant of bromocriptine. The intolerance is likely to occur with initiation of treatment or when the dose is increased. Administration via the vaginal route may reduce the incidence of side effects and avoid first-pass metabolism by the liver (Kletzky 1989; Ginsburg 1992). This route of administration has no effect on sperm activity (Carranza-Lira 1999). Bromocriptine is also available in a long-acting form for intramuscular injection. The safety of bromocriptine on ovulation, pregnancy and fetal development is well-documented in humans (Turkalj 1982; Krupp 1987; Majumdar 2013; Hurault-Delarue 2014). Approximately 25% of patients are resistant to bromocriptine (Verhelst 1999).

Cabergoline is an ergot-derived dopamine agonist, which has low affinity for $D_1$ dopamine receptors and high affinity for $D_2$ receptors (Del Dotto 2003). Cabergoline is better tolerated than bromocriptine with approximately 10% of patients resistant, and 80% of patients who are resistant to bromocriptine may achieve prolactin normalization on cabergoline (Colao 1997; Verhelst 1999). Rat studies show cabergoline has a direct inhibitory effect on pituitary lactotroph cells. Cabergoline is a long-acting dopamine agonist with less side effects and better patient compliance. It is frequently used as a second-line agent in the management of hyperprolactinemia when bromocriptine is ineffective. A dose of 0.25 mg twice per week is usually adequate for hyperprolactinemia. Beltrame 1996 proved that cabergoline was not teratogenic or embryotoxic in mice and rabbits and did not affect the latter phase of gestation or parturition in the rat. The safety of cabergoline on embryo-fetal development was been proved in humans (Robert 1996; Auriemma 2013; Hurault-Delarue 2014).

Quinagolide is a non ergot-derived dopamine agonist with a chemical structure similar to apomorphine. It acts specifically and with high affinity on $D_2$ dopamine receptors and has little affinity for $D_1$ dopamine receptors (Closse 1988). Both the specificity and the non-ergot nature of quinagolide reduce the risk of side effects. Patients are typically initiated at a dose of 0.025 mg/day and increased to a dose of 0.075 mg/day. If necessary, the quinagolide dose can be increased up to a maximum dose of 0.3 to 0.6 mg/day (Barlier 2006). No teratogenic effects of quinagolide during early pregnancy in humans have been reported in a relatively small number of pregnancies (Homburg 1990; Morange 1996; Schultz 2000).

Terguride is the C9-10 dihydrogenated derivative of lisuride. It has mixed dopaminergic-antidopaminergic activity with fewer side effects. Lisuride is a dopamine agonist with a high affinity for the dopamine $D_2$. Pergolide is an ergoline-based dopamine receptor agonist. Quinagolide is also a selective, $D_2$ receptor agonist.

### How the intervention might work

The possible mechanisms of dopamine agonist on preventing recurrent miscarriage are as follows (Seppälä 1976; Lecomte 1997).

1. It acts on ovaries directly to promote synthesis of steroid hormones.
2. It acts on pituitary to promote synthesis of steroid hormones.
3. It acts on hypothalamus to promote secretion of luteinizing hormone-releasing hormone (LHRH).
4. It inhibits secretion of prolactin.

### Why it is important to do this review

Although recurrent miscarriage affects only 1% to 3% of women, it influences the well-being and psychosocial status of patients. Hirahara and Bussen reported hyperprolactinemia was found in around 36% of recurrent miscarriage patients (Hirahara 1996; Bussen 1999). Due to the fact that prolactin levels are important in maintaining early pregnancy and hyperprolactinemia is relatively common in women who miscarry, hyperprolactinemia may be linked to recurrent miscarriage (Ando 1992; Hirahara 1996; Hirahara 1998; Bussen 1999). In clinics, doctors tend to examine the patients' serum prolactin levels when no cause of recurrent miscarriages has been found, and treatment is given when hyperprolactinemia is found. However, the pathophysiologic mechanisms and effects of treatments on a future pregnancy are still incompletely understood. Accordingly, we set out to determine the benefits and harms from dopamine agonists in preventing a future miscarriage given to women who had idiopathic hyperprolactinemia (including occult hyperprolactinemia) with a history of recurrent miscarriages.

## OBJECTIVES

To assess the effectiveness and safety of different types of dopamine agonists in preventing future miscarriage given to women diagnosed with idiopathic hyperprolactinemia, with a history of recurrent miscarriage.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials (RCTs) examining the effect of dopamine agonists on preventing future miscarriage, given to women who were diagnosed with idiopathic hyperprolactinemia (including occult hyperprolactinemia), with a history of recurrent miscarriages, were eligible for inclusion in this review. There were no restrictions on language and publication status. RCTs using a cluster-randomized were eligible for inclusion in this review, but none were identified.

Quasi-RCTs, RCTs using a cross-over design and studies published in abstract form only (where insufficient information was available) were not eligible for inclusion in this review.

#### Types of participants

Women who were diagnosed with idiopathic hyperprolactinemia (including occult hyperprolactinemia) with a history of recurrent miscarriages.

#### Types of interventions

1. Dopamine agonists alone versus placebo/no treatment.
2. Dopamine agonists combined with other therapy versus other therapy alone.

#### Types of outcome measures

##### *Primary outcomes*

1. Rate of miscarriage (before 20 weeks of gestation).
2. Rate of live birth (term delivery or premature delivery rate).

##### *Secondary outcomes*

1. Rate of conception.
2. Proportion of reduction in serum prolactin levels.
3. Rate of serum prolactin normalization.
4. Rates of adverse maternal effects: nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms.
5. Rates of adverse fetal outcomes: birth defects, low birthweight, and developmental disabilities.

### Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

#### Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist (30 June 2016)

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies).

### Searching other resources

We searched the citation lists of retrieved studies. We did not apply any language or date restrictions.

## Data collection and analysis

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

### Selection of studies

Two review authors (Chen and Fu) independently examined titles and abstracts from the initial search in order to identify studies that met the inclusion criteria. The full text of those studies thought to fulfil the inclusion criteria were retrieved. We resolved any disagreement through discussion.

### Data extraction and management

We designed a format extract data. For the eligible study, two review authors (Chen and Fu) extracted data using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2014) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

### Assessment of risk of bias in included studies

Two review authors (Chen and Fu) independently assessed risk of bias for the included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. We did not require consultation with a third party, but will use this strategy if required when conducting future updates of the review.

#### *(1) Random sequence generation (checking for possible selection bias)*

We described for the one included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

#### *(2) Allocation concealment (checking for possible selection bias)*

We described the method used to conceal the allocation sequence and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non opaque envelopes, alternation; date of birth);
- unclear risk of bias.

#### *(3.1) Blinding of participants and personnel (checking for possible performance bias)*

We described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We had determined that studies would be considered at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

#### *(3.2) Blinding of outcome assessment (checking for possible detection bias)*

We described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

#### *(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)*

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (where less than 20% of the randomized population was excluded);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

#### *(5) Selective reporting bias*

We described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study fails to

include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

***(6) Other sources of bias***

We described any important concerns we had about other possible sources of bias.

We assessed whether the included study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

***(7) Overall risk of bias***

We made explicit judgements about whether the included study was at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. In future updates, if more studies are included, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

***Assessment of the quality of the evidence using the GRADE approach***

The quality of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons.

1. Rate of miscarriage.
2. Rate of live birth.
3. Rate of conception.
4. Proportion reduction in serum prolactin levels.
5. Rate of serum prolactin normalization.
6. Rates of adverse maternal effects: nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms.
7. Rates of adverse fetal outcomes: birth defects, low birthweight, and developmental disabilities.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

**Measures of treatment effect**

For binary data, we presented results as risk ratio with 95% confidence intervals. If appropriate, in future updates of this review, for continuous date, we will use the mean difference to combine trials if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome but use different methods.

**Unit of analysis issues**

***Cluster-randomized trials***

No cluster-randomized trials were identified. However, in future updates of the review, if identified, we will include cluster-randomized trials in the analyses along with individually-randomized trials.We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesis the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit through undertaking sensitivity analyses - see Sensitivity analysis.

***Cross-over trials***

Cross-over trials are not eligible for inclusion as this particular design is inappropriate for our review question.

***Other unit of analysis issues***

In future updates, if we include trials with more than two treatment groups, we will assess the most appropriate way to include the data (such as combining groups to create a pair-wise comparison or selecting the most appropriate pair of interventions and excluding the others).

**Dealing with missing data**

For the included study, we noted levels of attrition. In future updates, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses, and all participants were analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

**Assessment of heterogeneity**

In future updates, we will assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$ and $Chi^2$ statistics. We will regard heterogeneity as substantial if an $I^2$ is greater than 30% and either the $T^2$ is greater than zero, or there is a low P value (less than 0.10) in the $Chi^2$ test for heterogeneity.

### Assessment of reporting biases

In future updates of this review, if there are 10 or more studies, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If we detect asymmetry by a visual assessment, we will perform exploratory analyses to investigate it.

### Data synthesis

As only one study was included, we did not combine data in a meta-analysis. In future updates, we will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing among trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of $T^2$ and $I^2$.

### Subgroup analysis and investigation of heterogeneity

We did not carry out subgroup analyses because that there was only one included study and insufficient information. If appropriate in future updates of this review, we will investigate heterogeneity using subgroup analyses and sensitivity analyses. We will carry out the following subgroup analyses if required.

1. Different types of dopamine agonists (e.g. comparisons between bromocriptine, cabergoline, and quinagolide).
2. Routes of supplementation (e.g. oral versus vaginal).
3. Dosage of supplementation (e.g. for bromocriptine, < 7.5 mg/day versus > 7.5 mg/day).
4. Level of serum prolactin on admission (e.g. prolactin > 100 mg/mL versus < 100 mg/mL).

We will use the following outcomes in subgroup analysis: rates of live births (term delivery or premature delivery); rates of miscarriage.

We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the $Chi^2$ statistic and P value, and the interaction test $I^2$ value.

### Sensitivity analysis

We only identified a single study for inclusion in this review. In future updates of this review, we will conduct sensitivity analyses to investigate the following effects.

1. Inclusion/exclusion of trials with "no intervention" as the control group.
2. Inclusion/exclusion of trials at high risk of bias, as determined the risk of allocation concealment.
3. Inclusion/exclusion of trials with high levels of missing data.
4. Fixed-effect/random-effects analyses for outcomes with statistical heterogeneity.
5. To examine the effect of the randomization unit (where we combine cluster-RCTs along with the individually-randomized trials).

Outcomes in the sensitivity analysis will include rates of miscarriage and rates of live births (term delivery or premature delivery).

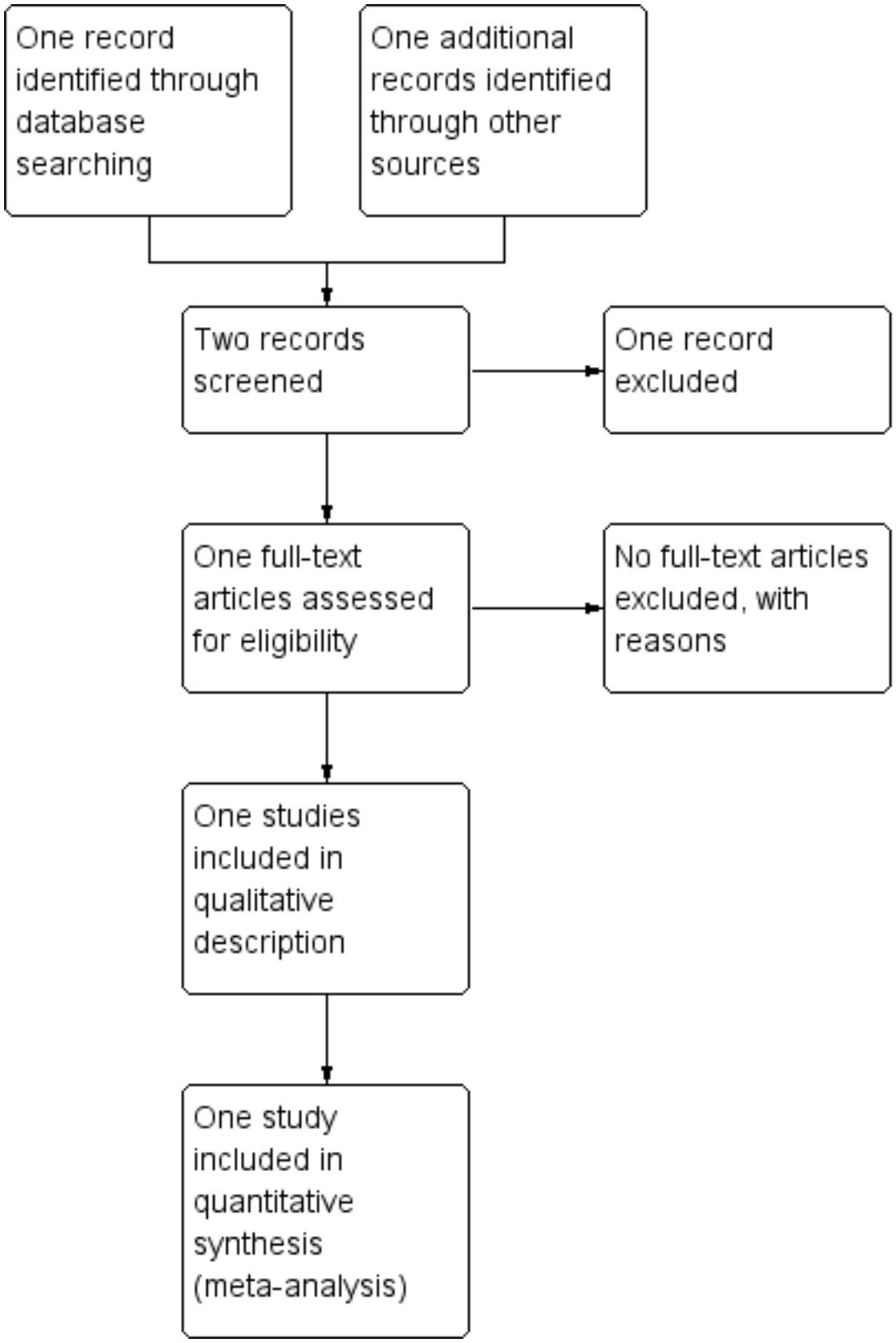
## RESULTS

## Description of studies

### Results of the search

See: Figure 1.

**Figure 1. Study flow diagram.**




The search retrieved just two reports, one was screened out at the title stage and one was included (Hirahara 1998).

### Included studies

#### *Study design and setting*

We included one parallel-design randomized controlled trial (Hirahara 1998) in this review. Hirahara 1998 was a single-centre study, conducted at the recurrent spontaneous abortion clinic at Yokohama City University Hospital in Japan.

#### *Participants*

Forty-eight women were enrolled after assessment for eligibility (24 in the intervention group and 24 in the no treatment control group). The women (aged 24 to 40 years) were diagnosed with idiopathic hyperprolactinemia and had a history of two to four spontaneous miscarriages. Twenty-four women had occult hyperprolactinemia (12 in the intervention group and 12 in the non treatment control group).

#### *Interventions*

Hirahara 1998 compared the use of bromocriptine (2.5 mg to 5.0 mg/day until the end of the ninth week of gestation) versus no treatment (control).

#### *Outcomes*

Outcomes were divided into primary and secondary, as listed above. Primary outcomes were reported, including rates of miscarriage and live birth. Live birth was not specified as term delivery or preterm delivery in this study. For secondary outcomes, conception and serum prolactin levels were assessed, while adverse effects on mother (nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms) and adverse fetal outcomes (birth defects, low birthweight, and developmental disabilities) were not reported.

#### *Follow-up*

Women were followed during the treatment period and a subsequent 12-month observation period.

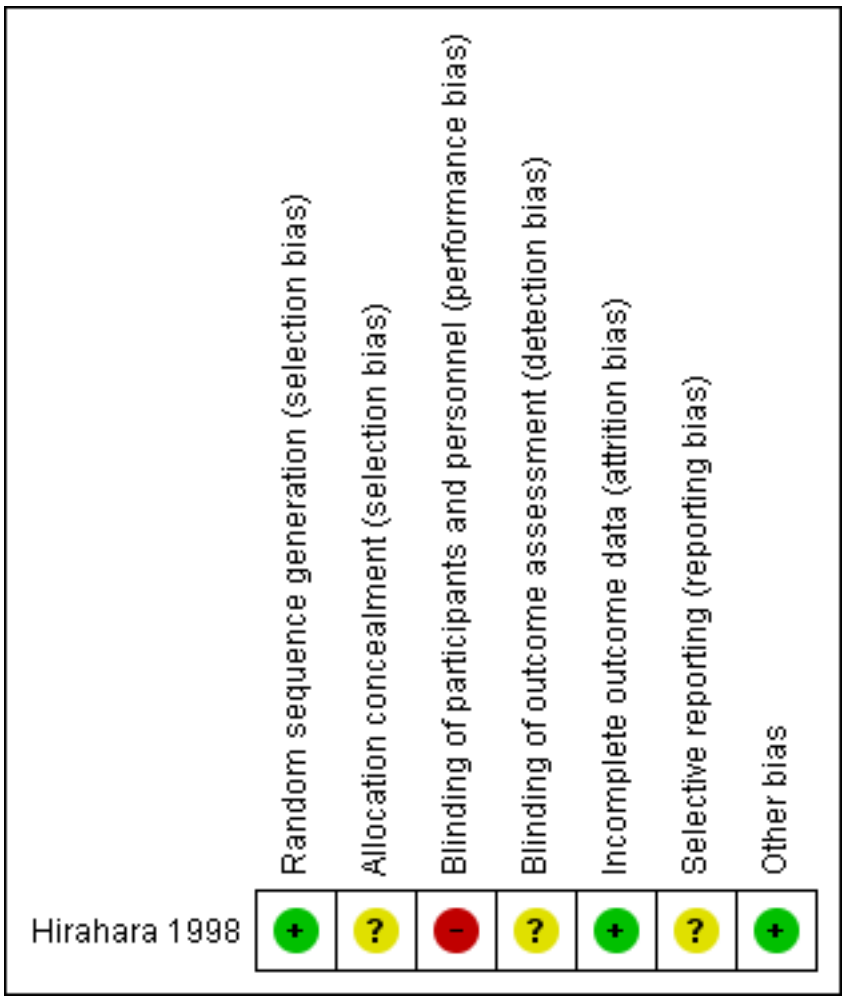
### Excluded studies

There are no excluded studies.

## Risk of bias in included studies

The included study was judged as being at a high risk of bias overall. See: Figure 2 for 'Risk of bias' assessment in our included study. For detailed descriptions of each risk of bias, see Characteristics of included studies.

**Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**



### Allocation

Hirahara 1998 used a computer-generated randomization process (low risk of bias), but it did not mention whether allocation concealment was used (unclear risk of bias).

### Blinding

Hirahara 1998 did not use placebo and was thus deemed to be at high risk of performance bias. The blinding of outcome assessment was not mentioned and we therefore rated the study as being at unclear risk of detection bias. We did not consider that blinding was likely to influence findings for the primary review outcome (miscarriage and live birth). However for some subjective secondary outcomes (maternal adverse effects such as nausea, headache, et al.), blinding status could potentially affect findings.

### Incomplete outcome data

In Hirahara 1998, two women in the control group dropped out of the study after randomization. The reasons for dropouts were not explained in the trial report. The remaining 46 women were followed up and included in the analysis. The low rate of missing data (4.2%) was considered to represent a low risk of attrition bias.

### Selective reporting

We intended to compare the protocols with published trials to assess reporting bias, however no protocol was available for the included study. So we compared the methods and results sections of the trial. Each outcome discussed in the methods sections was reported by Hirahara 1998 except that serum prolactin levels were only reported for pregnant women. The trial failed to report adverse events as an outcome, only mentioning that women in the trial who became pregnant did not require further medications or hospitalization. Hence we assessed this included study as of unclear risk for selective reporting bias.

### Other potential sources of bias

There were no significant differences between the groups with regard to the baseline of included women (Hirahara 1998). We found no potential sources of within-study bias in this study.

## Effects of interventions

See: **Summary of findings for the main comparison** Bromocriptine versus no treatment for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history

Only one trial (Hirahara 1998) compared bromocriptine versus no treatment. There were no randomized controlled trials focusing on other types of dopamine agonists such as cabergoline and quinagolide. Meta-analysis was not possible and we did not carry out subgroup analyses as there is only one included study.

### Dopamine agonist (bromocriptine) alone versus no treatment (control) - comparison 1

The Hirahara 1998 trial (46 women were analyzed) compared bromocriptine (2.5 mg to 5.0 mg/day until the end of the ninth week of gestation) versus no treatment.

#### *Primary outcomes*

##### 1.1 Miscarriage

Compared to no treatment control, oral bromocriptine was associated with a reduction in future miscarriage (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.09 to 0.87, 46 participants, *low-quality evidence*) in women with idiopathic hyperprolactinemia (Analysis 1.1). See Summary of findings for the main comparison.

##### 1.2 Live birth

There was no clear difference with regard to live births among women in the bromocriptine group compared to the rate of live births in the no treatment control group (RR 1.50, 95% CI 0.93 to 2.42, 46 participants, *very low-quality evidence*) (Analysis 1.2). See Summary of findings for the main comparison.

#### *Secondary outcomes*

##### 1.3 Conception

There was no difference with regard to the rate of conception (RR 0.92, 95% CI 0.77 to 1.09, 46 participants, *very low-quality evidence*) between the bromocriptine and no treatment groups. See Analysis 1.3 and Summary of findings for the main comparison.

##### 1.4 Proportion reduction in serum prolactin levels and rate of serum prolactin normalization

The included study only reported the serum prolactin levels in pregnant women and could not be analyzed further in this review.

##### 1.5 Adverse maternal effects

None of our prespecified maternal adverse effects (nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms) were reported in the included study.

##### 1.6 Adverse fetal outcomes

None of our pre-specified fetal adverse effects (birth defects, low birthweight, and developmental disabilities) were reported in included study. The trial authors only mention that no women who became pregnant required further medications or hospitalizations.

# DISCUSSION

## Summary of main results

This review assessed the effects of dopamine agonists preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. However, only one randomized controlled trial (RCT) recruiting 48 patients met our inclusion criteria. The included study was judged as being at a high risk of bias. *Low-quality evidence* from this study showed bromocriptine was effective in preventing future miscarriage. However, *very low-quality evidence* also showed that live birth and conception rates were similar between the bromocriptine group and the no treatment group. The included study did not report adverse effects (nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms; fetal outcomes: birth defects, low birthweight, and developmental disabilities). The trial authors do mention that there were no further medications or hospitalizations required for women in the trial who became pregnant.

We did not identify any randomized controlled trials focusing on other types of dopamine agonists such as cabergoline and quinagolide.

### Overall completeness and applicability of evidence

To the best of our knowledge, this is the only systematic review on dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. Very little on this topic was identified, with only one trial meeting our inclusion criteria. This study was conducted in 1998 in Japan. The definition of hyperprolactinemia in this trial (above 10 ng/mL; n = 48) was different from the most widely accepted definition nowadays (above 25 ng/mL). Trial authors justified their inclusion criteria by stating that their definition was based on data from 96 healthy menstruating women and 367 infertile women. This included study did not report on adverse effects of the intervention for the mother and her baby.

### Quality of the evidence

There are multiple sources of potential bias in the included study and we rated the evidence for the review outcomes of miscarriage as low quality and live birth and conception as very low quality (see Summary of findings for the main comparison).

Limitations can largely be attributed to the small number of studies and participants. There was only one trial that met our inclusion criteria. This trial recruited small numbers of women. Details of allocation concealment and blinding of assessment were not given. Lack of blinding would be less important for objective outcomes such as miscarriage, live birth, and conception. A number of this review's secondary outcomes regarding safety were not reported in the included trial (maternal outcomes: nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms; fetal outcomes: birth defects, low birthweight, and developmental disabilities). Consequently, no definitive conclusions could be made from this review about the efficacy and safety of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage.

We assessed outcomes with the GRADE methodology. Miscarriage was assessed as of low quality due to risk of bias concerns in the one trial contributing data (no description of allocation concealment, lack of blinding and possible reporting bias) and to imprecision (effect estimates were based on small sample size and few events). Live births and conception were assessed as of very low quality due to same risk of bias concerns in study design and to imprecision (with a wide 95% confidence interval consistent with either benefit or harm), and a small sample size.

### Potential biases in the review process

In the process for conducting a systematic review, biases could include publication bias, selective outcome reporting bias, selective analysis bias and fabrication bias (Higgins 2011). We prepared this review using Cochrane methodology, and were guided by both the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the standard methods of the Cochrane Pregnancy and Childbirth Group. Two review authors independently performed study selection, data extraction and assessment of risk of bias. We used standardized data extraction forms.

### Agreements and disagreements with other studies or reviews

The evidence in this review is consistent with the findings of a non-randomized study by Rossi 1995, which reported 103 pregnancies in 64 women (49 with bromocriptine treatment and 15 with no treatment). In that study, the rate of miscarriage was 18% in bromocriptine group and 16% in no treatment group, while term delivery was 72% and 48%, respectively.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is currently insufficient evidence to guide clinical practice concerning the use of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. This is due to the inclusion of only one small randomized controlled trial (RCT).

### Implications for research

This systematic review has identified the need for well-designed, larger RCTs to confirm and extend the findings of the trial reviewed here. Many questions remain unanswered. Some important considerations for future research are as follows.

1. Well-designed RCTs with large sample size are needed.
2. Adverse effects, especially fetal outcomes should be assessed.
3. Effectiveness of various dopamine agonists including bromocriptine, cabergoline and quinagolide should be measured.

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# REFERENCES

## References to studies included in this review

**Hirahara 1998** *{published data only}*

Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. *Fertility & Sterility* 1998;**70**(2):246-52.

## Additional references

**Aisaka 1993**

Aisaka K, Kanadas S, Tsuzuki H, Toriya Y, Kokuho K, Tamechika S, et al. A study with diagnostic standard of occult hyperprolactinemia (OHP) and the effect of bromocriptine administration. *Nippon Naibunpi Gakkai Zasshi* 1993;**69**(9):1017-27.

**Ando 1992**

Ando N, Gorai I, Hirabuki T, Onose R, Hirahara F, Minaguchi H. Prolactin disorders in patients with habitual abortion. *Nihon Sanka Fujinka Gakkai Zasshi* 1992;**44**(6):650-6.

**Asukai 1993**

Asukai K, Uemura T, Minaguchi H. Occult hyperprolactinemia in infertile women. *Fertility and Sterility* 1993;**60**:423-7.

**Auriemma 2013**

Auriemma RS, Perone Y, Di Sarno A, Grasso LF, Guerra E, Gasperi M, et al. Results of a single-center observational 10-year survey study on recurrence of hyperprolactinemia after pregnancy and lactation. *Journal of Clinical Endocrinology and Metabolism* 2013;**98**(1):372-9.

**Barlier 2006**

Barlier A, Jaquet P. Quinagolide--a valuable treatment option for hyperprolactinaemia. *European Journal of Endocrinology* 2006;**154**(4):187-95.

**Beltrame 1996**

Beltrame D, Longo M, Mazué G. Reproductive toxicity of cabergoline in mice, rats, and rabbits. *Reproductive Toxicology* 1996;**10**(6):471-83.

**Ben-David 1983**

Ben-David M, Schenker JG. Transient hyperprolactinemia: a correctable cause of idiopathic female infertility. *Journal of Clinical Endocrinology and Metabolism* 1983;**57**:442-4.

**Bussen 1999**

Bussen S, Siitterlin M, Steck T. Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. *Human Reproduction* 1999;**14**(1):18-20.

**Carranza-Lira 1999**

Carranza-Lira S, Gonzalez-Sanchez JL, Martinez-Chequerj C. Vaginal bromocriptine administration in patients with hyperprolactinemia. *International Journal of Gynecology & Obstetrics* 1999;**65**(1):77-8.

**Chahal 2008**

Chahal J, Schlechte J. Hyperprolactinemia. *Pituitary* 2008;**11**:141-6.

**Closse 1988**

Closse A, Camps M, Wanner A, Palacios JM. In vivo labeling of brain dopamine D2 receptors using the high-affinity specific D2 agonist (3H)CV 205–502. *Brain Research* 1988;**440**:123-32.

**Colao 1997**

Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. *Journal of Clinical Endocrinology and Metabolism* 1997;**82**(3):876-83.

**Daya 2004**

Daya S. Evidence-based management of recurrent miscarriage: optimal diagnostic protocol. *International Congress Series* 2004;**1266**:318-27.

**Del Dotto 2003**

Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. *Clinical Pharmacokinetics* 2003;**42**:633-45.

**Dlugi 1998**

Dlugi AM. Hyperprolactinemic recurrent spontaneous pregnancy loss: a true clinical entity or a spurious finding?. *Fertility and Sterility* 1998;**70**(2):253-5.

**Friesen 1970**

Friesen H, Guyda, Hardy J. The biosynthesis of human growth hormone and prolactin. *Journal of Clinical Endocrinology and Metabolism* 1970;**31**(6):611-24.

**García-Enguídanos 2002**

García-Enguídanos A, Calle ME, Valero J, Luna S, Domínguez-Rojas V. Risk factors in miscarriage: a review. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2002;**102**:111-9.

**Gillam 2006**

Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. *Endocrine Reviews* 2006;**27**:485-534.

**Ginsburg 1992**

Ginsburg J, Hardiman P, Thomas M. Vaginal bromocriptine–clinical and biochemical effects. *Gynecological Endocrinology* 1992;**6**:119-26.

**Glezer 2014**

Glezer A, Bronstein MD. Prolactinomas, cabergoline, and pregnancy. *Endomcrine* 2014;**47**(1):64-9.

**Higgins 2011**

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

**Hirahara 1996**

Hirahara F. The clinical management for recurrent spontaneous abortion. *Nihon Sanka Fujinka Gakkai Zasshi* 1996;**48**:169-72.

**Homburg 1990**

Homburg R, West C, Brownell J, Jacobs HS. A double-blind study comparing a new non-ergot, long-acting dopamine agonist, CV 205–502, with bromocriptine in women with hyperprolactinaemia. *Clinical Endocrinology* 1990;**32**:565-71.

**Huang 2007**

Huang I, Gibson M, Peterson CM. Endocrine disorders. In: Berek JS editor(s). Berek and Novak's Gynecology. 14th Edition. Philadelphia: Lippincott Williams and Wilkins, 2007:1069-136.

**Hurault-Delarue 2014**

Hurault-Delarue C, Montastruc JL, Beau AB, Lacroix I, Damase-Michel C. Pregnancy outcome in women exposed to dopamine agonists during pregnancy: a pharmacoepidemiology study in EFEMERIS database. *Archives of Gynecology & Obstetrics* 2014;**290**(2):263-70.

**Katharina 2008**

Katharina TW. Progesterone for recurrent miscarriage: truth and deceptions. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2008;**22**:375-9.

**Kletzky 1989**

Kletzky OA, Vermesh M. Effectiveness of vaginal bromocriptine in treating women with hyperprolactinemia. *Fertility and Sterility* 1989;**51**:269-72.

**Kostál 1997**

Kostál M, Tosner J. The influence of latent hyperprolactinaemia on the levels of LH, FSH, E2 and T in the midfollicular phase of the cycle. *Archives of Gynecology & Obstetrics* 1997;**259**:65-8.

**Krupp 1987**

Krupp P, Monka P. Bromocriptine in pregnancy: safety aspects. *Klinische Wochenschrift* 1987;**65**(17):823-7.

**Lecomte 1997**

Lecomte P, Lecomte C, Lansac J, Gallier J, Sonier CB, Simonetta C. Pregnancy after intravenous pulsatile gonadotropin-releasing hormone in a hyperprolactinaemic woman resistant to treatment with dopamine agonists. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1997;**74**(2):219-21.

**Majumdar 2013**

Majumdar A, Mangal NS. Hyperprolactinemia. *Journal of Human Reproductive Sciences* 2013;**6**(3):168-75.

**Mancini 2008**

Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. *Endocrinology and Metabolism Clinics of North America* 2008;**37**(1):67-99.

**Melmed 2008**

Melmed S, Jameson JL. Disorders of the anterior pituitory and hypothalamus. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL editor(s). Harrison's Principles of Internal Medicine. 16th Edition. New York: McGraw Hill, 2008:2076-97.

**Melmed 2011**

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2011;**95**:4268-75.

**Molitch 2015**

Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. *European Journal of Endocrinology* 2015;**172**(5):R205-13.

**Morange 1996**

Morange I, Barlier A, Pellegrini I, Brue T, Enjalbert A, Jaquet P. Prolactinomas resistant to bromocriptine: long-term efficacy of quinagolide and outcome of pregnancy. *European Journal of Endocrinology* 1996;**135**:413-20.

**Mühlenstedt 1977**

Mühlenstedt D, Wuttke W. Prolactin and short luteal phase infertility. *Fertility and Sterility* 1977;**28**:373.

**Regan 1989**

Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;**299**:541-5.

**RevMan 2014 [Computer program]**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Robert 1996**

Robert E, Musatti L, Piscitelli G, Ferrari CI. Pregnancy outcome after treatment with the ergot derivative, cabergoline. *Reproductive Toxicology* 1996;**10**(4):333-7.

**Rossi 1995**

Rossi AM, Vilska S, Heinonen PK. Outcome of pregnancies in women with treated or untreated hyperprolactinemia. *European Journal of Obstetrics & Gynecology* 1995;**63**:143-6.

**Schenker 1992**

Schenker GJ. Stress and human reproduction. In: Klinmek R editor(s). Pre- and Perinatal Psycho-Medicine. Dream Krakow, 1992:80.

**Schultz 2000**

Schultz PN, Ginsberg L, McCutcheon IE, Samaan N, Leavens M, Gagel RF. Quinagolide in the management of prolactinoma. *Pituitary* 2000;**3**:239-49.

**Seppälä 1976**

Seppälä M, Ranta T, Hirvonen E. Hyperprolactinaemia and luteal insufficiency. *Lancet* 1976;**1**(7953):229-30.

**Stirrat 1990**

Stirrat GM. Recurrent miscarriage. *Lancet* 1990;**336**:673-5.

**Toth 2010**

Toth B, Jeschke U, Rogenhofer N, Scholzc C, Würfeld W, Thaler CJ, et al. Recurrent miscarriage: current concepts in diagnosis and treatment. *Journal of Reproductive Immunology* 2010;**85**(1):25-32.

**Turkalj 1982**

Turkalj I, Braun P, Krupp P. Surveillance of bromocriptine in pregnancy. *JAMA* 1982;**247**:1589-91.

**Tyson 1973**

Tyson JE, Fresen HG. Factors influencing the secretion of human prolactin and growth hormone in menstrual and gestational women. *American Journal of Obstetrics and Gynecology* 1973;**116**:377-87.

**Vance 1984**

Vance ML, Evans WS, Thorner MO. Drugs five years later. Bromocriptine. *Annals of Internal Medicine* 1984;**100**:78-91.

**Verhelst 1999**

Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *Journal of Clinical Endocrinology & Metabolism* 1999;**84**:2518-22.

**Wang 2012**

Wang AT, Mullan RJ, Lane MA, Hazem A, Prasad C, Gathaiya NW, et al. Treatment of hyperprolactinemia: a systematic review and meta-analysis. *Systematic Reviews* 2012;**1**:33.

**Webster 1999**

Webster J. Clinical management of prolactinomas. *Baillière's Clinical Endocrinology and Metabolism* 1999;**13**(3):395-408.

**Yamaguchi 1991**

Yamaguchi M, Aono T, Koike K, Nishikawa Y, Ikegami H, Miyake A, et al. Effects of nocturnal hyperprolactinemia on ovarian luteal function and galactorrhea. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1991;**39**:187-91.

**Yip 2003**

Yip S, Sahota D, Cheung L, Lam P, Haines C, Chung T. Accuracy of clinical diagnostic methods of threatened abortion. *Gynecologic and Obstetric Investigation* 2003;**56**(1):38-42.

## References to other published versions of this review

**Chen 2010**

Chen H, Lina H. Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD008883]

## CHARACTERISTICS OF STUDIES

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

**Hirahara 1998**

| | |
|---|---|
| Methods | Random allocation to 2 groups using a computer-generated random number table. |
| Participants | Inclusion criteria: women diagnosed with idiopathic hyperprolactinemia; had a history of 2 or more consecutive miscarriages without other etiologic factors; of normal weight (body mass index, 19 kg to 24 kg/m$^2$).<br><br>Exclusion criteria: women with prolactin disorders, endocrinologic abnormalities (e.g. luteal phase dysfunction, polycystic ovaries, LH hypersecretion, and thyroid hormone disorders or any other etiologic factors for recurrent spontaneous abortion). Hyperprolactinemic women who were taking medications that would affect serum prolactin levels were also excluded.<br><br>Enrollment: 48 women were allocated (24 intervention, 24 control) before conception. After enrollment, 2 women in control group dropped out of the study. The reason for dropout was not given. |
| Interventions | Intervention group (n = 24): before conception, bromocriptine (2.5 to 5.0 mg/day) was given to women in this group until the end of the 9th week of gestation in whom the serum prolactin levels and the responses to TRH were normalized.<br><br>Control group (n = 22): no treatment was given.<br><br>46 women in total (42 pregnancies - 4/46 women did not conceive during the study period - 21/24 in the bromocriptine group and 21/22 in the no-treatment control. |
| Outcomes | Rates of live birth.<br><br>Rates of miscarriage. |

**Hirahara 1998** *(Continued)*

| | |
|---|---|
| | Rates of conception.<br>Prolactin levels. |
| Notes | Setting: the study took place in Yokohama City University Hospital, Japan.<br>Date of study: not stated.<br>Follow-up: women were followed during the treatment and observation for 1 year. Prolactin levels were collected weekly between 4th and 12th gestational weeks during early pregnancy.<br>Source of funding: supported in part by the National Cooperative Prevention Program for Mental and Physical Disorders, Ministry of Health and Welfare of Japan. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random schedules generated by computer. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding not reported. There was no placebo control (control was no treatment). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 2 women in control group dropped out of the study after enrollment. The reasons for dropouts were not explained. The rate of missing data was 4.2%. |
| Selective reporting (reporting bias) | Unclear risk | The trial protocol was not available. Each outcome discussed in the methods sections was reported up except that serum prolactin levels were only reported in those pregnant women. The trial report does not mention specific adverse events as |
| Other bias | Low risk | None apparent. |

LH: luteinizing hormone
TRH: thyrotropin-releasing hormone

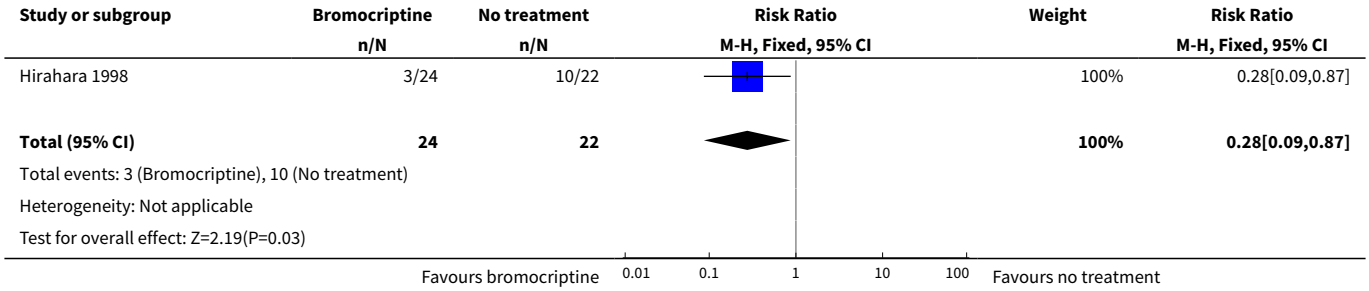
## DATA AND ANALYSES

### Comparison 1. Dopamine agonists alone versus no treatment

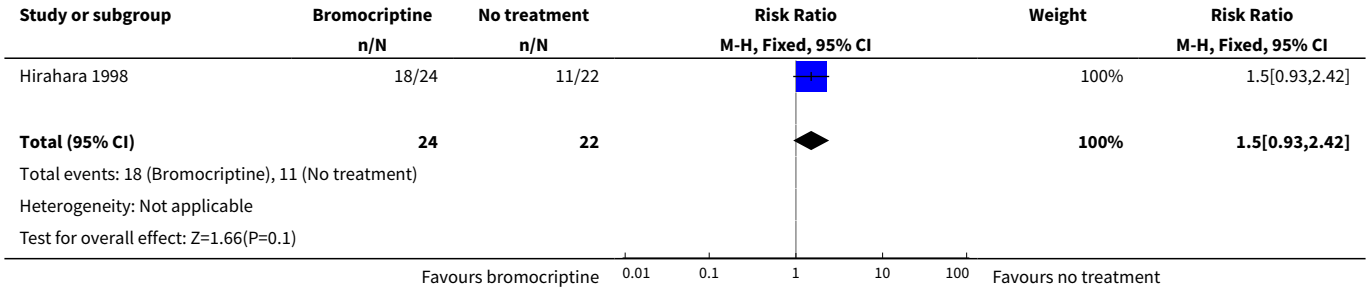
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Miscarriages | 1 | 46 | Risk Ratio (M-H, Fixed, 95% CI) | 0.28 [0.09, 0.87] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2 Live births | 1 | 46 | Risk Ratio (M-H, Fixed, 95% CI) | 1.5 [0.93, 2.42] |
| 3 Conception | 1 | 46 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.77, 1.09] |

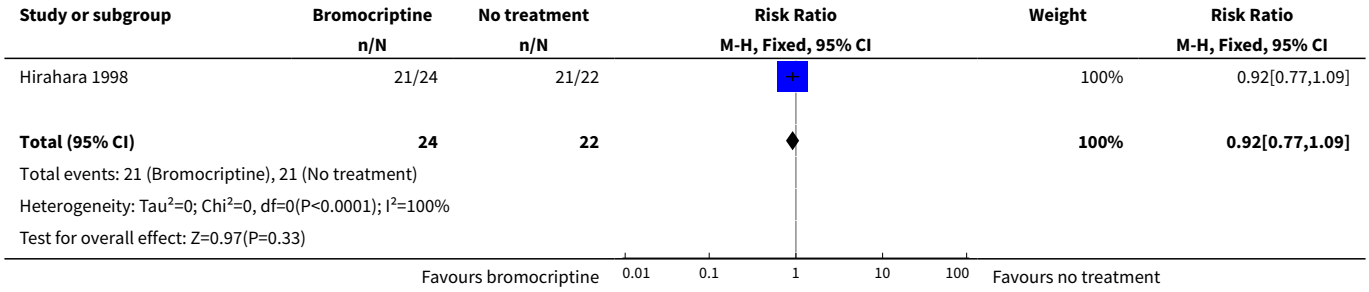
**Analysis 1.1. Comparison 1 Dopamine agonists alone versus no treatment, Outcome 1 Miscarriages.**




**Analysis 1.2. Comparison 1 Dopamine agonists alone versus no treatment, Outcome 2 Live births.**




**Analysis 1.3. Comparison 1 Dopamine agonists alone versus no treatment, Outcome 3 Conception.**




## CONTRIBUTIONS OF AUTHORS

Hengxi Chen was responsible for developing the protocol, searching for trials, assessing the quality of trials, extracting data, analyzing data and developing the review.

Jing Fu was responsible for searching for trials, assessing the quality of trials, and extracting data.

Wei Huang was responsible for amending the review.

## DECLARATIONS OF INTEREST

Hengxi Chen - none known.

Jing Fu - none known.

Wei Huang - none known.

## SOURCES OF SUPPORT

### Internal sources

- West China Second University Hospital, China.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between our published protocol (Chen 2010) and the full version of the review.

**Background** - we have updated the background.

**Methods/types of intervention** - we expanded this to include intervention versus no treatment.

**Methods/types of outcomes/secondary outcomes** - we have edited some secondary outcomes:

'Safety: teratogenicity, developmental disabilities of fetus, et al.' has been replaced by two secondary outcomes -

5. Rates of adverse maternal effects: nausea, vomiting, headache, vertigo, fatigue, hypotension, arrhythmia, and psychotic symptoms

6. Rates of adverse fetal outcomes: birth defects, low birthweight, and developmental disabilities

**Methods/search methods** - this section has been updated to reflect the current standard search methods of Cochrane Pregnancy and Childbirth.

**Methods/data collection and analysis** - we have used the GRADE approach to assess the quality of the body of evidence.

**Methods/sensitivity analysis** - we have added that, in future updates, we will carry out sensitivity analysis to investigate the effect of the randomization unit (if relevant).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Abortion, Habitual [etiology] [*prevention & control]; Bromocriptine [*therapeutic use]; Dopamine Agonists [*therapeutic use]; Hyperprolactinemia [complications] [*drug therapy]; Live Birth; Randomized Controlled Trials as Topic

### MeSH check words

Female; Humans; Pregnancy