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Systematic review

Inadvertent P-hacking among trials and systematic reviews of the effect of progestogens in pregnancy? A systematic review and meta-analysis

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Background Progestogens have been evaluated in numerous trials and meta-analyses, many of which concluded they were effective. However, two large trials PROMISE and OPPTIMUM have recently concluded that progesterone was ineffective. This raises the possibility that earlier studies and reviews had been biased by either selective publication or selective choice of outcomes, so called "P-hacking".

Objectives To compare the findings all progestogen trials and systematic reviews with those of trials with pre-registered primary outcomes which avoided selective outcome reporting.

Search strategy Search of PubMed, the Cochrane Library and trial registries. Registration PROSPERO CRD42016035303.

Selection criteria Systematic reviews of randomised trials comparing progestogen with placebo in pregnancy and the individual trials included in those reviews. The subset of trials reporting a pre-registered primary outcome were compared with the totality of trials and reviews.

Data collection and analysis For reviews all outcomes were included. For individual trials all outcomes reported in the systematic reviews were included. For the comparison group we recorded the registered primary outcome from trials that were either registered before they started, or registered during the recruitment phase and also double blind.

Main results Nineteen of twenty-nine meta-analyses concluded that progestogens were effective. Twenty-two trials reported their pre-registered primary outcomes. There was no effect of progesterone on primary registered dichotomous outcome RR 1.00 (95% CI 0.94–1.07). Only one of the 22 showed a nominally statistically significant benefit.

Author's conclusions When evaluated in registered double-blind trials with analysis restricted to predefined primary outcomes, progestational agents in pregnancy are ineffective.

Keywords Miscarriage, outcome switching, P-hacking, pregnancy loss, preterm birth, progestogen.

Tweetable abstract Progestogens to prevent pregnancy loss, an example of P-hacking.

Linked article This article is commented on by CM Chung et al, p. 1016 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14648. This article is also commented by J van't Hooft and KS Khan on page 1017. To view this mini commentary visit https://doi.org/10.1111/1471-0528.14647.

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Introduction

There is increasing concern that many published results of randomised trials are biased by selective reporting of trials with positive results, and by researchers, often inadvertently, selectively reporting nominally statistically significant outcomes.[1] This latter practice has been called P-hacking. There are several ways researchers can fall foul of P-hacking by misreporting the true effect sizes in their studies. These include monitoring data accrual and stopping a trial if an analysis yields a significant *P*-value or using different statistical analyses, data eligibility criteria,

outcomes and treatment groups before deciding which to report post-analysis. Double blinding and trial registration mitigate P-hacking by researchers pre-specifying their primary outcome and analysis plans, only conducting the analyses when the trial has ended and the code is broken.[2]

Systematic reviewers are equally at risk if they fail to pre-specify their primary outcomes instead choosing to publish when the data look interesting. They can try to minimise the problem by including all available trials, and registering protocols before starting work, but the former policy risks including more low quality biased trial data and the latter is difficult in a mature field where the results of the major trials and reviews are already widely known.[2]

Meta-analyses are only as good as those data they use, but their results influence treatment decisions, health policy and the direction of future research. P-hacking is important because the publication of false positives leads to the adoption of treatments which are ineffective to patients.

Studies of progestogens to prevent pregnancy complications provide a good setting to measure this effect because there have been many trials and at least twenty-nine meta-analyses. The aim of this work was to compare the findings all progestogen trials and systematic reviews with those of trials with pre-registered primary outcomes which avoided selective outcome reporting to explore the impact of P-hacking.

Methods

The review was conducted following the PRISMA statement,[3] and the protocol prospectively registered with PROSPERO CRD42016035303.

Search strategy

We searched PubMed, the Cochrane Library and World Health Organisation recognised publicly-registered trials registries[4] from inception to August 2016 for terms related to progestogen, pregnancy and trials (Appendix S1). Two authors (MP and JT) independently conducted the first screening of potentially relevant records based on titles and abstract and then independently performed the final selection of included trials based on full text evaluation. Citation tracking was also performed on included studies and relevant systematic reviews. Consensus between the two reviewers was used to resolve any disagreement.

Study selection

The total study group

This included all systematic reviews with meta-analyses of double-blind randomised controlled trials comparing the efficacy of progestogens versus placebo in pregnancy to improve any pregnancy outcome. We analysed all outcomes reported by these systematic reviews. For individual trials we identified all trials included in at least one meta-analysis, and analysed all outcomes for which data had been included in at least one meta-analysis.

The preregistered trial outcome group

We included trials which were prospectively listed in a World Health Organisation recognised publicly-registered trials registry with a predefined primary outcome, and which either achieved their pre-specified sample size, or were both double blind, and failed to achieve their sample size for logistical reasons unrelated to the trial result. The primary outcome had to be included in the trial report. Trials were excluded if they were not registered or registered late. There were no restrictions for languages or publication date.

Data extraction and quality assessment

Two reviewers (MP and JT) independently assessed the reviews and trials for inclusion. For systematic reviews three reviewers (MP, RH and NA) extracted all outcomes, the number of trials used for each meta-analysis, whether the point estimate favoured progesterone or placebo and if the 95% confidence interval crossed 1. For RCTs study characteristic data were extracted by two reviewers (MP, and JT) (details of participants, intervention, registered primary outcome with intention to treat analysis and the number of secondary outcomes) for the included trials. Two reviewers (MP and JGT) compared each manuscript with the trial registration and excluded trials that did not reported the registered primary outcome. For trials with dichotomous outcomes we extracted the number of participants and events in the progestogen and control groups. For trials with a continuous primary outcome we extracted means, standard deviations, and sample sizes for the pre-registered primary outcome measure. Consensus was used to resolve any disagreement.

Data analysis

For trials, we ensured consistency in direction of effect by converting the primary outcomes. For example, "reaching 24 weeks with a live baby" was converted to "failing to reach 24 weeks with a live birth". Summary measures used were risk ratio and mean difference using a random effects model. For trials reporting only the median and interquartile range; we assumed that the former equalled the mean and that the standard deviation was 1.35 times the latter. RevMan version 5.3. (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to generate figures and summaries.

Results

Study selection

Our search results yielded 3753 records, and after excluding duplicates we screened 2467 titles and abstracts (Figure 1). This process finally revealed 194 relevant studies.

Systematic reviews

We identified 29 systematic reviews (Table S1). These reported results of 93 trials, and 537 outcomes.

Randomised trials

We identified 93 randomised controlled trials. These trials together reported 1804 outcomes.

Registered trials

We identified about 60 progestogen trials included in one or more registries. Of these at least 30 were discontinued or remain unpublished (data not shown). Of the remainder three unblinded trials were registered during recruitment.[5–7] Four published trials were excluded because they had been registered after trial completion[8–11] and two because they did not report the registered primary outcome[12,13] (Table S2). One trial registration NCT00830765 was used for two trials.[12,13] The first a randomised controlled trial of progestogen for preterm premature rupture of membranes and the second a trial of progestogen in women with arrested preterm labour. The primary outcome was updated in the registry from "the aim is to compare progesterone to a placebo to ascertain if there is a reduction in preterm birth among patients receiving the active drug" to "weeks gestation at birth among patients receiving the active drug" after the first study had been published in 2013. Neither paper reported either of the two registered primary outcomes. Instead they reported "interval from study entry to delivery" and "delivery before 37 weeks" respectively. There were other inconsistencies between registry and publication versions. Both trials were excluded.

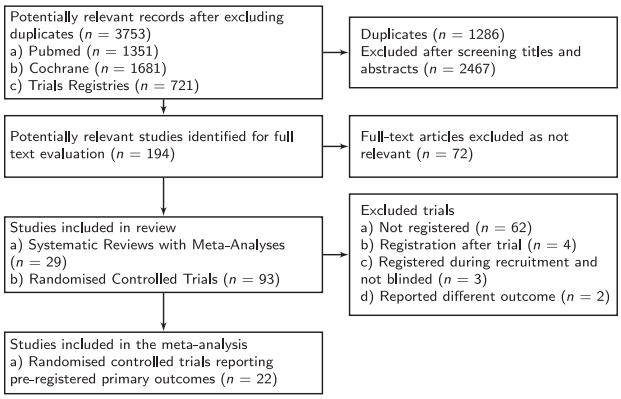

Figure 1. Study selection process.

This left 22 randomised controlled trials with primary outcomes which were judged not to be at risk of P-hacking. (Table 1). The full list of unregistered trials identified is shown in Appendix S2.

We identified one trial via PubMed registered with the Iranian Registry of Clinical Trials.[14] We converted Persian calendar dates on the registry to Gregorian so they could be compared with the Gregorian dates in the published manuscript.

Study characteristics

Nineteen of twenty-nine meta-analyses concluded that progestogens were effective for a variety of indications (Table S1).

Overall the 29 meta-analyses (MA) reported 537 MA outcomes together with 95% confidence intervals (CI). Of these 372 favoured progestogen, 154 favoured control and 3 had an exact RR of 1. Of the MA outcomes which favoured progestogen 113 (30%) had a CI which excluded 1, i.e. were nominally statistically significant. Of the MA outcomes which favoured control, 145 (94%) had a CI which included 1.

The unregistered and late registered trials had 1782 outcomes reported in the various systematic reviews. Of these 618 favoured progestogen, 378 favoured control and 32 had an exact RR of 1. Of the individual trial outcomes which favoured progestogen 116 (19%) had a CI which excluded 1, i.e. were nominally statistically significant. Of the individual trial outcomes which favoured control, 366 (97%) had a CI which included 1 (Table S3).

Of the twenty-two included trials, 8113 participants were randomised. Nineteen trials reported data from 7125 patients evaluated the efficacy of progestogens in preventing or treating preterm birth[14–32] two trials (162 patients) studied the efficacy of progestogen in preterm pre labour rupture of membranes[33,34] and one trial (826 patients) investigated the efficacy of progestogen in preventing recurrent miscarriage.[35] The route of progestogen administration was equally divided, with eleven studies using intramuscular injection and eleven by the vaginal route. Twelve trials were prospectively registered before enrolment of the first participant. Thirteen trials were registered after the first patient had been recruited, nonetheless all of these studies were double blind and registered before unblinding after either achieving their sample size or stopped for an unrelated reason.

Nineteen included trials reported a dichotomous primary outcome. Three studies reported continuous primary outcomes of either interval from inclusion until delivery[25,27] or gestational age at birth.[28]

Synthesis of results

In our meta-analysis, restricted to trials reporting predefined primary registered outcomes there was no effect of

Table 1. Registered trials reporting pre-specified primary outcomes

	Population	Progestogen used	Registered primary outcome	Reported primary outcome
Awwad, 2015[29] NCT00141908	PTB (twins)	17-OHP	The frequency of delivery prior to completed 37 weeks of gestation (259 days)	Prolongs gestation beyond 37 weeks of gestation
Caritis, 2009[30] NCT00099164	PTB Prevention (Triplets)	17-OHP	Delivery prior to 35 weeks 0 days gestation	Delivery or fetal loss prior to 35 weeks
Combs, 2010[32] NCT00163020	PTB (triplets)	17-OHP	A composite for neonatal morbidity	A composite for neonatal morbidity
Combs, 2011[34] NCT01119963	PPROM	17-OHP	Interval from PROM until delivery of 34 weeks 0 days, whichever comes first	The rate of continuing the pregnancy until 34.0 weeks of gestation
Combs, 2015[33] NCT01119963	PPROM	17-OHP	Interval from PROM until delivery of 34 weeks 0 days, whichever comes first	The rate of continuing the pregnancy until 34.0 weeks of gestation
Coomarasamy, 2015[35] ISRCTN92644181	Recurrent miscarriage	Vaginal	Live births beyond 24 weeks	Live birth after 24 weeks of gestation
Grobman, 2012[16] NCT00439374	PTB	17-OHP	Delivery prior to 37 weeks	Delivery prior to 37 weeks 0 days of gestation
Hassan, 2011[19] NCT00615550	PTB	Vaginal	Number of participants with birth ≤32 6/7 weeks' gestation	Preterm birth before 33 weeks of gestation
Lim, 2011[20] ISRCTN40512715	PTB	17-OHP	Composite neonatal morbidity	Composite adverse neonatal outcome
Martinez de Tejada, 2015[18] NCT00536003	PTB	Vaginal	Preterm birth before 37 weeks of gestation	Delivery before 37 weeks of gestation
Norman, 2009[17] ISRCTN35782581	PTB (twins)	Vaginal	Proportion of women in each group delivering before 34 weeks' gestation	Delivery or intrauterine death before 34 weeks' gestation
Norman, 2016[15] ISRCTN14568373	PTB	Vaginal	Delivery <34 weeks of gestation	Fetal death or birth before 34 weeks' gestation
O'Brien, 2007[21] NCT00086177	PTB	Vaginal	Frequency of delivery ≤32 weeks	Preterm birth at ≤32 weeks of gestation
Palacio, 2013[22] NCT00646802	PTB	Vaginal	Proportion of deliveries before week 34 of gestation	Preterm delivery before 34.0 pregnancy weeks
Rode, 2011[23] NCT00329914	PTB (twins)	Vaginal	The incidence of delivery at <34 weeks' gestation	Delivery before 34 weeks' gestation
Rouse, 2007[24] NCT00099164	PTB (twins)	17-OHP	Delivery prior to 35 weeks 0 days of gestation	Delivery or fetal death before 35 weeks of gestation
Senat, 2013[25] NCT00331695	PTB	17-OHP	Interval between inclusion and delivery	Time from randomisation to delivery
Serra, 2013[31] NCT00480402	PTB	Vaginal	'Preterm birth rate (<37 weeks)'	'Preterm birth rate (<37 weeks of gestation)'
Sharami, 2010[14] IRCT138706051096N1	PTB	Vaginal	Preterm delivery before 37 weeks of gestation	Preterm birth before 37 weeks
Tan, 2012[26] ISRCTN22145023	PTB	17-OHP	Delivery within 48 hours	Delivery within 48 hours of trial entry
Winer, 2015[27] NCT00331695	PTB	17-OHP	Interval between inclusion and delivery	Time from randomisation to delivery
Wood, 2012[28] NCT00343265	PTB	Vaginal	Gestational age	Gestational age at delivery

17-OHP, intramuscular 17α-hydroxyprogesterone; PTB, preterm birth.

progestogen on. For dichotomous outcome RR 1.00 (95% CI 0.94–1.07) and continuous outcome RR −1.39 (95% CI −7.47 to 4.69). This was also the case when grouping trials by indication or when combining indications (Figures 2 and 3).

The number of secondary outcomes reported by each trial ranged from 2 to 103. These included outcomes relating to pregnancy, gestation at delivery, birthweight, maternal and neonatal morbidity.

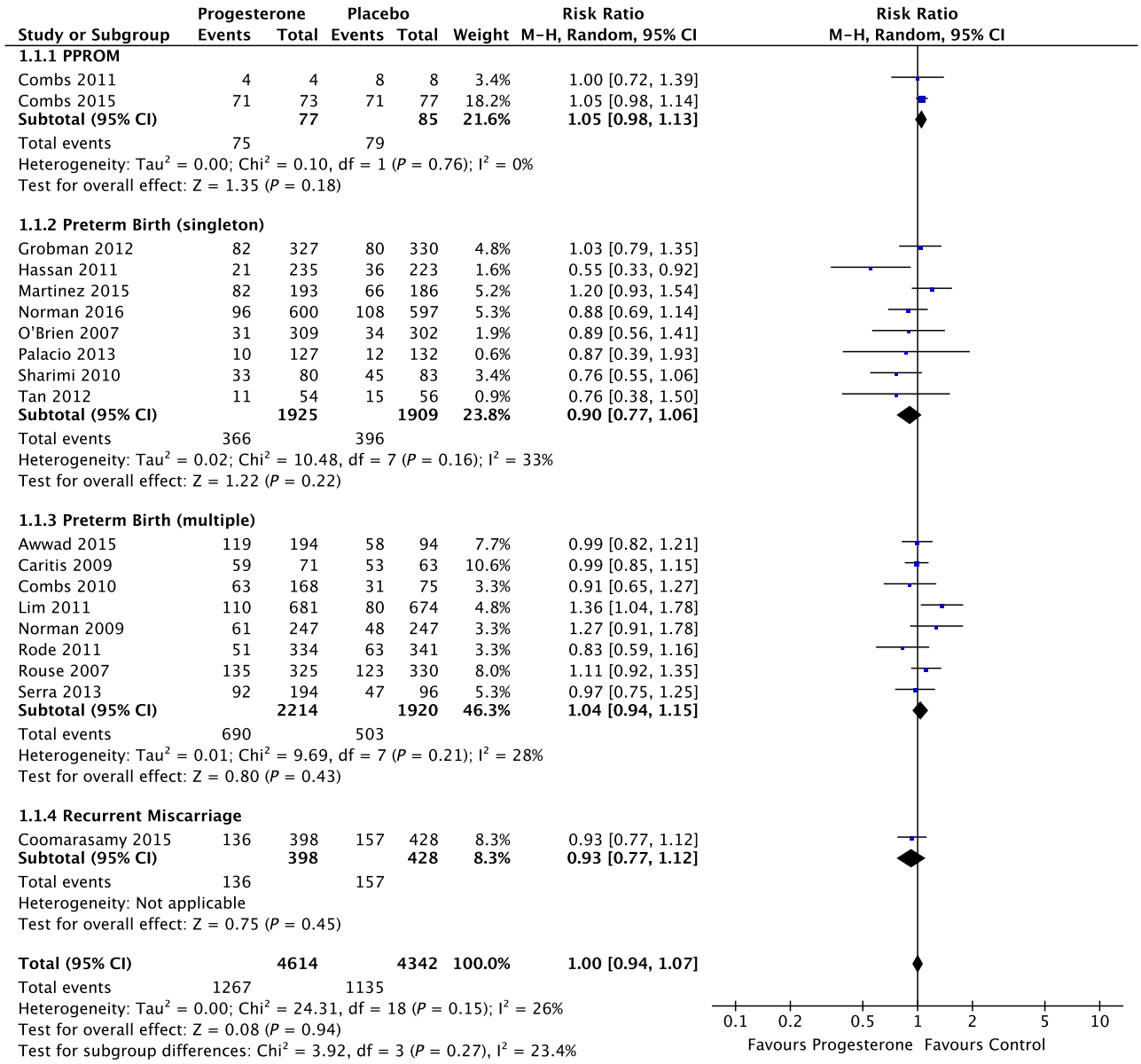

Figure 2. Progesterone versus placebo: primary registered dichotomous outcome.

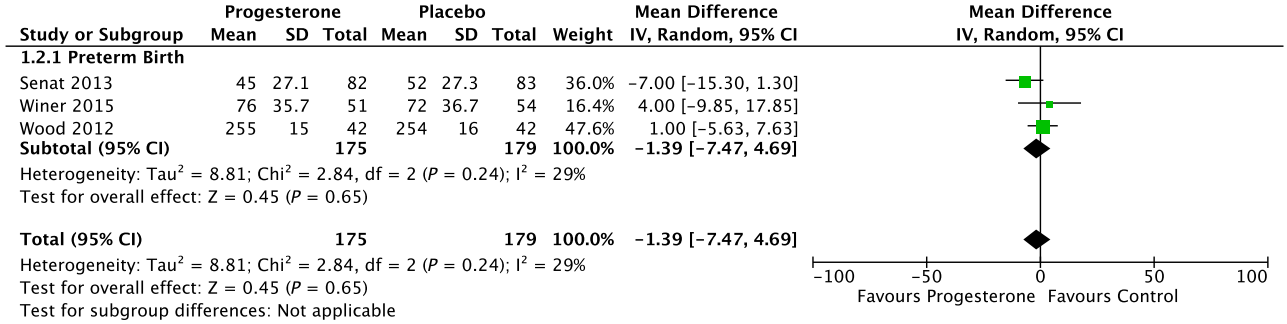

Figure 3. Progesterone versus placebo: primary registered continuous outcome.

Discussion

Main findings

When evaluated in registered double-blind trials with analysis restricted to predefined primary outcomes, progestational agents in pregnancy are ineffective for all indications they have been tested for. One trial appeared to show a marginally significant result according to conventional tests of significance.[19] This could well be a chance effect, on average one out of 20 perfectly conducted randomised trials will show an effect at the conventional $P = 0.05$ level of statistical significance. We also found the two well known trials by Meis et al.[36] and Fonseca et al.[10] were unregistered and registered late respectively.

It was disappointing that we identified more systematic reviews of this drug in pregnancy ($n = 29$) than prospectively registered trials ($n = 22$). We hope readers will forgive us adding to the former number and that in future more research effort will be spent on well conducted primary research.

Strengths and limitations

The strength of this study is our restriction to those trials conducted with the highest methodological rigour. Although we may have missed some unregistered trials it is unlikely we missed any registered ones; by definition trials not found by our search of trial registries were unregistered. The limitations are that including different clinical conditions, gestations at treatment and outcomes, albeit all treated with the same drug, is of more methodological than clinical significance. Nonetheless, we did not extract all reported outcomes from these trials. We only report those outcomes which made it into a systematic review.

Some readers may question our combining trials testing the effect of progestogen in different settings. The included studies are heterogeneous in terms of indication, clinical characteristics, inclusion criteria, primary outcomes all of which can affect the results of this systematic review. We agree that this may not be biologically or scientifically plausible, but we did so because our aim is primarily methodological. We have shown that when opportunity for P-hacking is removed, with one exception which would be expected by chance, progestogen trials in pregnancy give negative results.

The International Committee of Medical Journal Editors (ICMJE) recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication. Nonetheless, we also included trials registered during the recruitment phase. We reasoned that for a double blind trial, providing the blinding code had not been broken, this gave no opportunity for selective choice of outcome.

Interpretation

We chose not to present secondary outcomes and those from non-registered trials as the list would be too long. However, among 29 previous meta-analyses (Table S1), 19 concluded that progestogens are effective and a further review stated that it may be effective with a need for caution. Only seven reviews concluded that progestogen was ineffective. It is possible these conflicting findings are due to population differences or progestogen preparation. However, we believe the most likely reason for the difference is that many non-registered clinical trials silently switched outcomes. Without prospective trial registration it is impossible to prove this for any individual trial. The Centre for Evidenced-based Medicine Outcome Monitoring Project (COMPare) has been monitoring clinical trials for switched outcomes in the top five medical journals (NEJM, JAMA, The Lancet, Annals of Internal Medicine, BMJ) since October 2015. To date, comparing 67 trials with their protocol or registry they have found 300 outcomes were not reported and 357 outcomes silently added.[37]

Our suggestion that progestogens are ineffective for preventing pre-term birth in general is likely to be widely accepted in light of the recent negative results from the high quality prospectively registered OPPTIMUM trial.[15] However, those who are tempted to suggest that progestogens work in singletons but not twins, that some types of progestogen work while others don't, that it works for prevention but not treatment, or in specific subgroups such as women with a short cervix, should think again. The evidence does not justify clinical use of progestogen, and we doubt it even justifies any more trials.

The exception is progestogen treatment for luteal phase support in assisted reproduction treatment. Despite all published systematic reviews suggesting that this is effective the evidence comes entirely from unregistered trials. A well conducted registered trial of progestogens for this indication is needed.

Conclusions

We believe by limiting meta-analyses to trials which cannot be P-hacked we have shown that selective outcome reporting is present in obstetrics and gynaecology. P-hacking is an important researcher-driven source of bias and through data driven meta-analyses its effects go beyond the interpretation of the original studies. Indeed the UK National Institute for Health and Care Excellence recommends progesterone for women with a short cervix at risk of preterm birth.[38] Clinicians and policy makers should be aware of this source of bias when making treatment decisions.

Disclosure of interests
None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship
Both Matthew Prior and Jim Thornton conducted the literature searches, designed the figures, study design, data extraction, data analysis, data interpretation and writing and redrafting or the manuscript. Rachel Hibberd and Nicole Asemota extracted data.

Details of ethics approval
Not required.

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None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

Appendix S2. Unregistered trials.

Table S1. Systematic reviews of progestational agents in pregnancy.

Table S2. Excluded registered trials.

Table S3. Summary of outcomes from systematic reviews and randomised controlled trials. ■

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