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Review

Progesterone for the prevention of preterm birth: A critical evaluation of evidence

Aravinthan Coomarasamy [a], Shakila Thangaratinam [b,*], Harry Gee [a], Khalid S Khan [a]

[a] *Education Resource Centre, Birmingham Women's Hospital, Metchley Park Road, Birmingham B15 2TG, UK*
[b] *Academic Unit of Obstetrics and Gynaecology, Keele University School of Medicine, University Hospital North Staffordshire, Stoke-on-Trent ST4 6QG, UK*

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Abstract

A systematic review of the literature identified nine randomised trials that evaluated the effects of progestational agents in the prevention of preterm delivery. These studies were of variable quality. Meta-analyses showed reductions in delivery rates before 37 weeks (OR 0.42, 95% CI 0.31–0.57) and 34 weeks (OR 0.51, 95% CI 0.34–0.77) as well as in respiratory distress syndrome (OR 0.55, 95% CI 0.31–0.96) with progestational agents. A cumulative meta-analysis showed that the treatment benefit for the outcome of delivery before 37 weeks exceeded the conventional level of statistical significance in 1975 ($p < 0.01$); by 1985, the p-value was <0.001, and by 2003, it was <0.0001. Another cumulative meta-analysis in which the studies were added to the pooled analysis by decreasing quality score showed significant benefit even when the analysis was limited to just the highest quality trials (OR 0.47, 95% CI 0.33, 0.66, $p < 0.0001$). An exploration of the applicability of the effects across various baseline risks using a L'abbe plot found that the benefit was consistent across a range of risks. A comprehensive review of both trial and observational data on harm did not show any demonstrable evidence of harm to mother and baby. Women at high risk of preterm birth should be recommended progestational agent therapy.

Keywords: Progestagens; Preterm birth

Contents

1. Introduction

Basic science evidence suggests that adequate concentration of progesterone in the myometrium counteracts the stimulatory activity of prostaglandins [1], lowers the

* Corresponding author. Tel.: +44 1782 55 2409; fax: +44 1216236922.
E-mail addresses: Shakila@doctors.org.uk, shaki_vt@yahoo.co.uk (S. Thangaratinam).

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concentration of oxytocin receptors [2], and inhibits the formation of gap junctions [3], raising the possibility of use of progestagens as agents to prevent preterm delivery. Over many decades, several randomised trials have shown a role for progestational agents in this context, although this has not resulted in their use in clinical practice. The reasons for the lack of use could be related to a perceived concern about the quality of the trials assessing these agents, as well as unawareness of the totality of existing evidence. Systematic reviews can help with both assessment of quality and presentation of the totality of evidence, although this is conditional to a large extent on the robustness with which the reviews are carried out.

A recent meta-analysis of randomised trials of progestational agents found them to be effective in reducing the risk of preterm delivery below 37 weeks [4]. However, it did not report on the quality of the included studies, nor explore the effect of the quality on the inferences. Moreover, the study failed to report on outcomes such as delivery rates before 34 weeks, which is a clinically more relevant endpoint than the 37 weeks threshold. This is because delivery before 34 weeks gestation accounts for three-quarters of neonatal mortality and one-half of long term neurological impairment in children [5]. Additionally, before clinicians could recommend, and women accept, progestational agent therapy, the applicability of the evidence and the safety of the drug need to be established.

We, therefore, carried out a systematic review with conventional as well as cumulative meta-analyses, firstly to explore the size and significance of the effects as trials accumulated over time, and secondly to evaluate the impact of quality of trials on effects. Furthermore, we assessed the applicability of the evidence to women at various baseline risks, and reviewed the evidence for safety of progestational agents.

2. Methods

We searched MEDLINE (1966–2004), EMBASE (1980–2004), Cochrane Library (2004:3), and SCISEARCH (1974–2004) for relevant citations. A combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one indexing progesterone ('progesterone', 'progestational hormones', 'progestational agents' and 'progest$') and the other indexing preterm birth ('preterm', 'premature', 'early labo(u)r' and 'pret$'). These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations.

Studies were selected if the target population was women with risk factors for preterm birth, the therapeutic intervention was progesterone or a progesterone metabolite (synthetic progestagens were excluded), and the studies were of randomised design. Studies in which the population was exclusively multiple pregnancies were excluded [6].

The selected studies were assessed for methodological quality using the components of study design that are

Table 1
Quality of trials included in the systematic review on the use of progestagens for the prevention of preterm birth

Study	Randomisation and concealment	Blinding	Description of withdrawals	Follow-up (%)	Quality score [26]
[22]	Adequate randomisation using random number table; concealment adequate with consecutive sealed envelopes	Double blind	Yes	91	5
[15]	Adequate randomisation by computer generated sequence; adequate concealment	Double blind	Yes	99	5
[24]	Adequate randomisation using random number table; adequate concealment	Double blind	Yes	100	5
[19]	Inadequate randomisation by last digit of registration number; concealment inadequate	Double blind	Yes	99	2
[23]	'Randomised': details not given; concealment unreported	Double blind	Yes	100	2
[18]	'Random double blind fashion': details not given; concealment unreported	Double blind	Yes	86	2
[21]	'Randomised': details not given; concealment unreported	Not known	Yes	100	1
[20]	Inadequate randomisation by alternate placement in two groups; concealment inadequate	Double blind	Yes	54	2
[25]	Inadequate randomisation by alternate assignment to each trial arms in one centre; ''at random'' in the other centre, but details not given; concealment unreported	None	Yes	100	1

related to internal validity [7]. Information on the adequacy of randomisation, concealment, blinding, description of withdrawals, and follow-up rates was sought. Odds ratios from individual studies were pooled using fixed and random effects models [8,9]. Heterogeneity of treatment effects was evaluated graphically using forest plot [9] and statistically using Chi-square test [10]. Exploration of the causes of heterogeneity was planned using variation in features of the population, intervention, outcome and study quality. To assess for publication bias, we performed a funnel-plot analysis [11], using Egger's test [12] to evaluate for asymmetry. In addition to conventional meta-analysis, we performed a *cumulative* meta-analysis in which the meta-analysis is

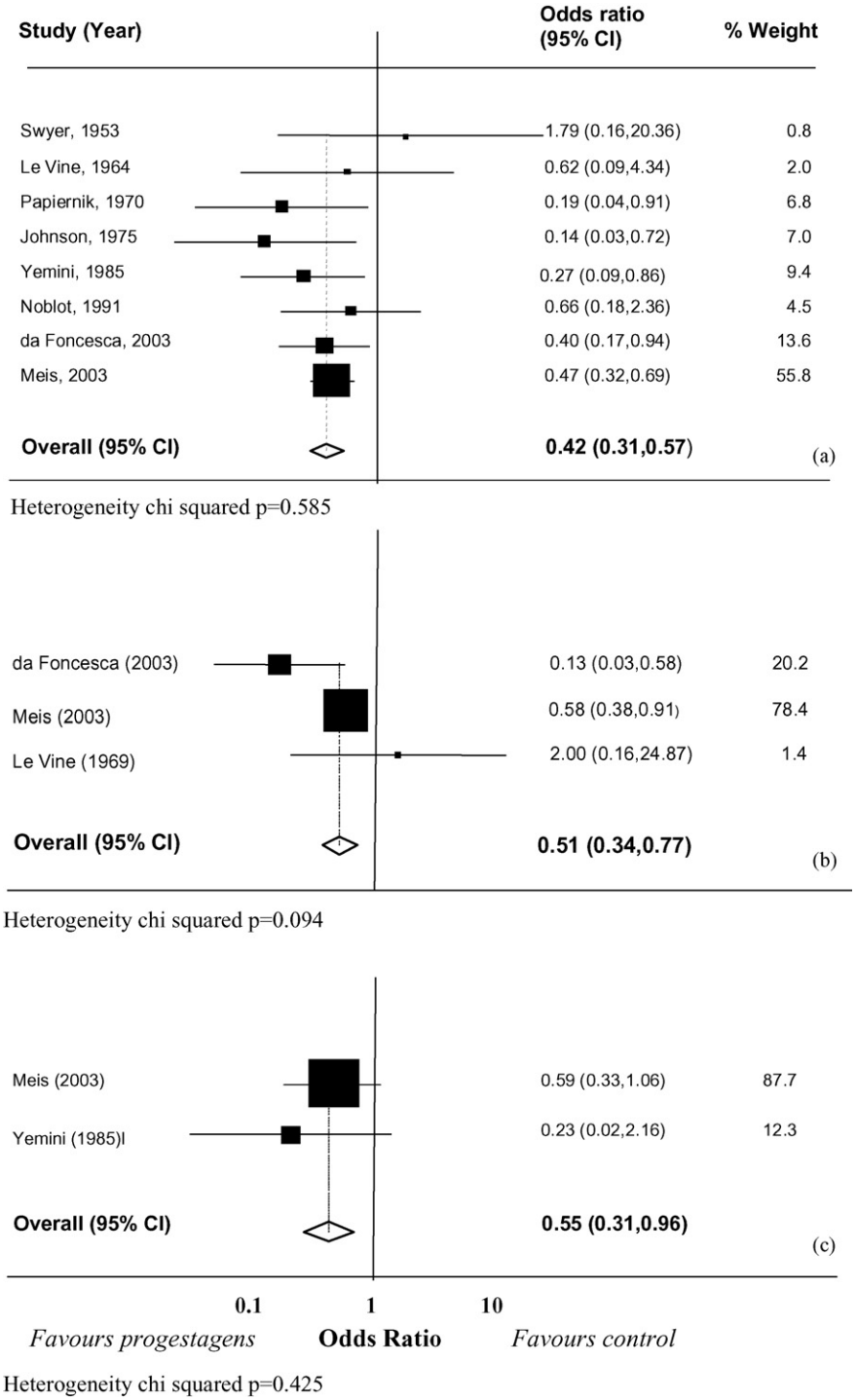

Fig. 1. Meta-analysis of randomised trials evaluating the effectiveness of progestational agents in the reduction of (a) delivery before 37 weeks, (b) delivery before 34 weeks, and (c) respiratory distress syndrome.

updated whenever a new relevant trial becomes available for inclusion in the review [13]. Such analysis allows the retrospective identification of the point in time when a treatment effect reached conventional levels of statistical significance [14]. In another *cumulative* meta-analysis, we started with the highest quality studies, and added lesser quality studies progressively, to explore the effect of study quality on the results.

In some trials of progesterone, the baseline risks in the control arms have been found to be high [15], raising the issue of whether the evidence of effectiveness applies to populations in which the baseline risks may be substantially lower. Although there are several issues to be considered when assessing applicability and, ultimately, assessment of applicability is a clinical judgement, we have explored the concern over baseline risks by evaluating the size of effects across a range of baseline risks using L'Abbe plot. The L'Abbe plot graphs the event rate in the control group (i.e., the baseline risk) against the event rate in the treatment group, thus allowing a visual assessment of homogeneity of effects across a range of baseline risks [16]. All data were analysed using Stata 8.0 statistical package.

As the total number of patients who received progestagens was just over 500 in all the randomised trials in this review, it is unlikely to have unearthed rare adverse events. Moreover, as trials generally involve patients studied for a short period, they are not likely to detect delayed adverse events [17]. We, therefore, conducted a review for safety of non-synthetic progestational agents using the following words and their word variants in MEDLINE (1966–2004) and EMBASE (1988–2004) bibliographic databases: ('progesterone' or 'progestational hormones' or 'progestational agents' or 'progest$') and ('adverse effects' or 'complications' or 'side effects' OR 'harm') and ''pregnancy''.

3. Results

3.1. Systematic review of effectiveness of progestational agents

Nine studies were identified for inclusion in the review after examination of the full manuscripts of studies that satisfied the selection criteria. The effect of 17 hydroxy progesterone caproate was assessed in five studies [15,18–21], vaginal progesterone suppositories in two studies [22,23], oral progesterone in one study [24] and intramuscular progesterone pellets in one study [25]. The quality of the studies is presented in Table 1, where we have also scored each study for quality using Moher's criteria [26]. A table detailing the characteristics of the included studies can be obtained from the corresponding author.

Pooling of the results from the studies showed a significant benefit of progestational agents in reducing preterm delivery before 37 weeks (OR 0.42, 95% CI 0.31–0.57, Fig. 1a). A significant benefit was also observed for the clinically more relevant outcome of delivery before 34 weeks (OR 0.51, 95% CI 0.34–0.77, Fig. 1b). No heterogeneity was identified for both results (p values of 0.59 and 0.09 for deliveries before 37 and 34 weeks, respectively).

There was a significant reduction in respiratory distress syndrome (RDS) with the use of progestagens (OR 0.55, 95% CI 0.31–0.96, Fig. 1c). The results were again homogenous ($p = 0.425$). Funnel-plot analysis indicated that publication and related biases were unlikely (Egger's test, $p = 0.384$).

3.2. Cumulative meta-analysis by time

Cumulative meta-analysis by year of study showed that the beneficial effect of progestational agents in reducing

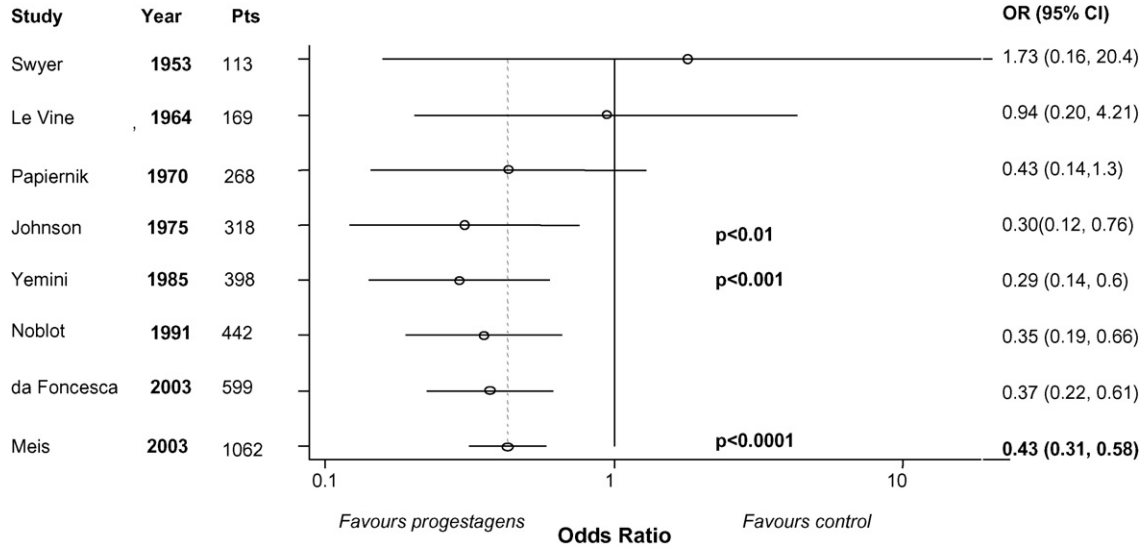

Fig. 2. Cumulative meta-analyses by year of study of randomised trials evaluating the effectiveness of progestagens in preventing delivery before 37 weeks.

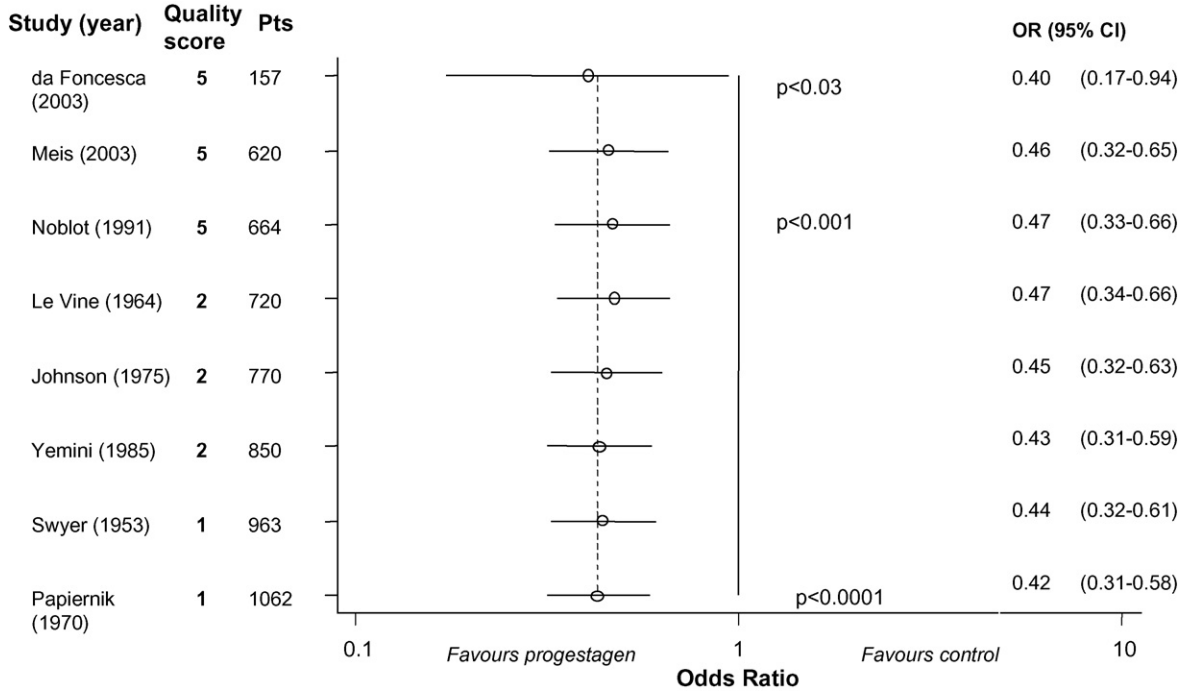

Fig. 3. Cumulative meta-analysis by quality score of randomised trials evaluating the effectiveness of progestagens in preventing delivery before 37 weeks.

preterm delivery before 37 weeks' gestation exceeded conventional level of statistical significance in 1975 ($p < 0.01$, OR 0.30, 95% CI 0.12–0.76); by 1985, the OR was 0.29 (95% CI 0.14, 0.6) with very high level of statistical significance ($p < 0.001$); and by 2003, the statistical significance was impressively high at $p < 0.0001$ with an OR of 0.43, 95% CI 0.31, 0.58 (Fig. 2). There has been a gradual narrowing of confidence intervals with increasing statistical certainty of benefit around a point estimate of about 60% reduction in the odds of preterm delivery with progestational agents.

3.3. Cumulative meta-analysis by study quality

Cumulative meta-analysis in which the studies were ranked by decreasing quality score showed that statistically significant benefit was shown even when we limited the analysis to the highest quality studies with the maximum quality score of 5 (OR 0.47, 95% CI 0.33, 0.66, $p < 0.001$, Fig. 3). Addition of the poorer quality trials simply improved the precision, but did not alter the inferences drawn from the highest quality studies alone.

3.4. Variation in effectiveness across different baseline risks

The L'Abbe plot which graphed event rate in the treated group against the control group for the outcome of delivery before 37 weeks, is presented in Fig. 4. This scatter plot shows that the magnitude of benefit from progestational agents does not change across a range of baseline risks (*x*-axis in Fig. 4). This supports the applicability of the findings to a wide range of populations with varying baseline risks. Naive regression analyses based on the L'Abbe plots were not done as they could suffer from regression to mean bias [27].

3.5. Safety of progestational agents

Our review of randomised trials of progestational agents for the prevention of preterm birth did not show any evidence of harm. A Cochrane review [28] which evaluated progestagens for various indications such as prevention of

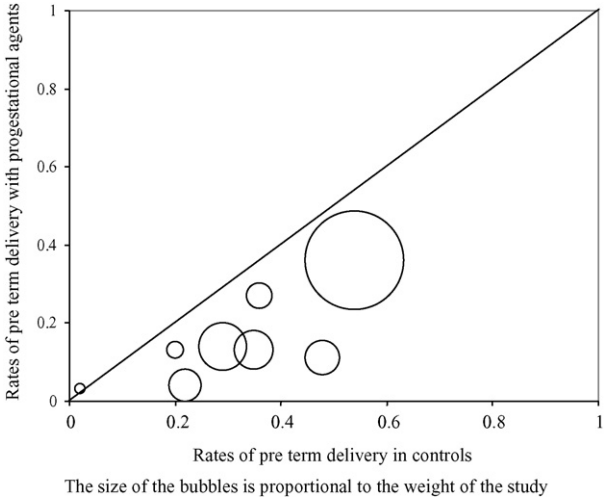

Fig. 4. L'Abbe plot of effect of progestational agents with varying baseline risk.

miscarriages and stillbirth identified 14 trials consisting of 1988 women, and found no evidence of harm to mother or baby, thus confirming our review findings. A systematic review of observational studies (both cohort and case–control studies) of first trimester sex hormone exposure identified 14 studies, consisting of 65,567 women [29]—the sex hormone in several of these 14 studies was progestagens alone or with other steroids and no harm, particularly any external genital malformation, was found in this review either. However, a recent case–control study suggested an association between progestagens and genital abnormalities, especially hypospadias [30]. This study had a small number of cases, a weak case–control design and included use of progestagens in early pregnancy, thus making the evidence unlikely to be relevant to the later use of progestagens in the prevention of preterm birth.

The extensive review by Brent has firmly ruled out any association between the use of progestagens and nongenital malformations [31].

4. Discussion

Our review shows that progestational agents have a large treatment effect in reducing the risk of a number of clinically relevant outcomes, especially delivery rates before 34 weeks and respiratory distress syndrome. The results were homogenous, and significant regardless of the statistical approach used for meta-analysis. In addition, there was no evidence of publication and related biases from funnel-plot analysis. Our cumulative meta-analysis of randomised trials shows that a significant benefit of progestagens in reducing preterm delivery was evident from 1975, and subsequent studies have increased our confidence to such a striking level that statistical uncertainty could not be cited as a reason for not using progestational agents. Reduced confidence in the quality of the older trials has been thought to be one of the reasons for not using progestagens. However, this could no longer be a reason as the findings from the highest quality recent randomised controlled trials concur with the older studies.

We did not include studies whose populations were exclusively women with multiple pregnancies. Earlier reviews showed that the consistent beneficial effect of progesterone was not observed in women with multiple pregnancies [4,32,33]. It might be that there are important factors other than what could be influenced by progestational agents that contribute to preterm birth in multiple pregnancies, and our review evidence is limited to singletons—a theory that needs further research. The exclusion of multiple pregnancies in two of the recent, good quality, large randomised trials [15,22] that showed significant benefit of progestagens lends support for this hypothesis.

In the existing review of progestational agents to prevent preterm birth, the authors have reported *average* numbers needed to treat (NNT) calculated the from pooled meta-analyses results. Such analyses can be seriously misleading [34], as NNTs are sensitive to changing baseline risks—the lower the risk, the higher NNTs, and the lower are our and women's expectations of benefit from treatment. Conversely, the higher the baseline risk, the lower the NNTs, and the higher are our and women's expectations of benefit from therapy, and the more inclined we would be to recommend, and women to accept therapy. NNTs will, therefore, need to be tailored according to baseline risks [35]. We have, therefore, given a range of NNTs appropriate for various baseline risk for the several outcomes in Table 2.

Table 2
Examples of numbers of women needed to be treated (NNTs) with progestational agents to prevent one case of various outcomes individualised according to baseline risks

Outcome	Historical risk factor	Baseline risk of the outcome (%)	Odds ratio (95% CI)	Number needed to be treated (95% CI)
Delivery before 37 weeks	Any previous preterm delivery	22 [37]	0.42 (0.31–0.57)	9 (7–12)
	Previous preterm delivery between 23 and 27 weeks	27 [37]		7 (6–10)
	Previous preterm delivery between 28 and 34 weeks	24 [37]		8 (7–11)
	Previous preterm delivery between 35 and 36 weeks	21 [37]		9 (7–13)
	Previous two preterm deliveries	40		5 (4–7)
	Transvaginal scan cervical length[a]			
	15 mm	64 [38]		5 (4–7)
	25 mm	50 [38]		5 (4–7)
Delivery before 34 weeks	Any previous preterm delivery	5 [37]		42 (31–90)
	Previous preterm delivery between 23 and 27 weeks	20 [37]	0.51 (0.34–0.77)	12 (8–26)
	Previous preterm delivery between 28 and 34 weeks	14 [37]		16 (11–35)
	Previous preterm delivery between 35 and 36 weeks	12 [37]		17 (12–37)
	Transvaginal scan cervical length[a]			
	15 mm	48 [38]		6 (4–15)
	25 mm	32 [38]		8 (5–19)

[a] The applicability to these groups is not yet explored or established.

There is no clear consensus on the dosage, route, or the release formulation, as well as the period of treatment with progestational agents. However, the largest high quality study [15] used intramuscular 17 hydroxy progesterone caproate at a dose of 250 mg weekly started between 16 to 20 weeks and continued until 36 weeks or delivery—this study was also associated with large treatment effects. Two other studies also used intramuscular 17 hydroxy progesterone caproate at same dosage as above, and found large treatment effects [18,19]. Another regime used in one of the recent and high quality study that again showed large treatment effects was vaginal progesterone suppositories of 100 mg every night [22]. We recommend either of these regimens.

We believe the very large treatment effects in clinically important outcomes of delivery before 34 weeks (50% reduction in odds) and respiratory distress syndrome (45% reduction in odds) cannot, and should not be ignored. Reluctance to use a very effective and safe therapy, which is based on level 1a evidence, is likely to cause untold harm, similar to the harm caused by the delay in the introduction of streptokinase therapy after myocardial infarction, or steroids in preterm birth [14,36].

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