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General obstetrics

Vaginal compared with intramuscular progestogen for preventing preterm birth in high-risk pregnant women (VICTORIA study): a multicentre, open-label randomised trial and meta-analysis

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Objective To compare the efficacy of two types of progestogen therapy for preventing preterm birth (PTB) and to review the relevant literature.

Design A multicentre, randomised, open-label, equivalence trial and a meta-analysis.

Setting Tertiary referral hospitals in South Korea.

Population Pregnant women with a history of spontaneous PTB or short cervical length (<25 mm).

Methods Eligible women were screened and randomised at 16–22 weeks of gestation to receive either 200 mg of vaginal micronised progesterone daily (vaginal group) or an intramuscular injection of 250 mg 17α-hydroxyprogesterone caproate weekly (IM group). Stratified randomisation was carried out according to participating centres and indications for progestogen therapy. This trial was registered at ClinicalTrials.gov (NCT02304237).

Main outcome measure Preterm birth (PTB) before 37 weeks of gestation.

Results A total of 266 women were randomly assigned and a total of 247 women (119 and 128 women in the vaginal and IM groups, respectively) were available for the intention-to-treat analysis. Risks of PTB before 37 weeks of gestation did not significantly differ between the two groups (22.7 versus 25.8%, $P = 0.571$). The difference in PTB risk between the two groups was 3.1% (95% CI −7.6 to 13.8%), which was within the equivalence margin of 15%. The meta-analysis results showed no significant differences in the risk of PTB between the vaginal and IM progestogen treatments.

Conclusion Compared with vaginal progesterone, treatment with intramuscular progestin might increase the risk of PTB before 37 weeks of gestation by as much as 13.8%, or reduce the risk by as much as 7.6%, in women with a history of spontaneous PTB or with short cervical length.

Keywords Preterm birth, prevention, progestogen, short cervical length.

Tweetable abstract Vaginal and intramuscular progestogen showed equivalent efficacy for preventing preterm birth before 37 weeks of gestation.

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Introduction

Preterm birth (PTB) is defined as birth before 37 completed weeks of gestation. It occurs in approximately 10% of all pregnancies worldwide,[1] and in nearly 7% of all births in Korea.[2] To effectively treat PTB, identifying the risk factors and preventing these are important. Risk factors of spontaneous PTB include a history of PTB, short cervical length (CL), multiple pregnancies, advanced maternal age, race, genetic factors, infectious diseases, smoking, uterine anomaly and a history of cervical conisation.[1,3] Among these risk factors, a history of spontaneous PTB and short CL are the most important predictors of PTB. The risk of recurrent PTB increases more than two-fold in women with a history of spontaneous PTB.[4,5] A short CL of <25 mm, as measured by transvaginal ultrasound during mid-trimester, is known to be the most reliable predictor for an increased risk of PTB.[6–8]

Progestogen supplement therapy is one of the few proven effective methods for preventing PTB in women with a history of spontaneous PTB or with short CL.[9–13] Progestogens are available in natural micronised or synthetic formulations for intramuscular, vaginal (tablet or gel) or oral administration.[14] Previous studies have reported that the injection of 17α-hydroxyprogesterone caproate (17-OHPC) can reduce recurrent PTB in women with a previous history of PTB.[15–17] Vaginal micronised natural progesterone therapy has also been found to be effective in preventing PTB in women with a history of PTB or with short CL in many trials,[18–22] but not in all.[23] The efficacy of progestogen to prevent PTB may vary depending on indication, type, administration route and dose of drug.[14] Data regarding which progestogen therapy is better for preventing PTB are insufficient, however.[24] The objective of this multicentre, randomised trial was to compare the efficacy of two different regimens of progestogen therapy: daily vaginal administration and weekly intramuscular injection. The results of our study are meta-analysed with previous randomised controlled trials that compared vaginal progesterone and intramuscular 17-OHPC for the prevention of PTB.

Methods

Study design

This was a multicentre, randomised, open-label, equivalence trial to compare the efficacy of two different regimens of progestogen therapy in preventing PTB in women with a history of PTB or with short CL. This study was conducted by the Preterm Birth Committee of the Korean Society of Maternal Fetal Medicine. Twenty-two tertiary referral hospitals in South Korea that offer universal screening for preterm delivery, by mid-trimester cervical length measurement, participated in the study. This study was approved by the Ministry of Food and Drug Safety of Korea and the Institutional Review Board of each participating centre. This trial was registered at ClinicalTrials.gov (NCT02304237). Participants were not involved in the development of the research and a core outcome set was not used when designing the trial.

Selection criteria

Pregnant women aged >20 years with a history of spontaneous PTB or with short CL (<25 mm), measured by transvaginal ultrasound, were screened at 15–22 weeks of gestation. Eligible women who gave informed consent to this study were randomised at 16–22 weeks of gestation to either daily self-administration of 200 mg vaginal micronised natural progesterone (vaginal group) or a weekly intramuscular injection of 250 mg of 17-OHPC (IM group). Spontaneous PTB was defined as delivery before 37 weeks of gestation as a result of preterm labour or preterm prelabour rupture of membranes. Exclusion criteria were multiple gestations, major congenital anomalies, elective prophylactic cervical cerclage at <16 weeks of gestation during the current pregnancy, previous iatrogenic PTB as a result of maternal or fetal indications, such as pre-eclampsia and fetal growth restriction, a history of progestogen therapy within 4 weeks before screening, chronic medical diseases, including diabetes, hypertension, epilepsy, heart disease, asthma, migraine, hepatic tumour, cholestatic jaundice, history or suspicion of cancer during the past 5 years, history or suspicion of thrombotic disease, gestational pemphigoid or porphyria, severe depression, being a heavy smoker or alcohol abuser and having hypersensitivity to progestogens. Participants who subsequently underwent an emergency cerclage after enrolment to this study were retained in the study and included in the intention-to-treat analysis.

Randomisation

We performed a block randomisation stratified by participating centres and indications of progestogen therapy as follows: history of spontaneous PTB and CL ≥25 mm (PTB history group), CL <25 mm without a history of

spontaneous PTB (short cervix group) and history of spontaneous PTB and CL <25 mm (both PTB history and short cervix group). We designed sequentially numbered scratch cards with concealed trial allocations (vaginal or IM progestogen) for randomisation. After obtaining informed consent, each participant scratched off the card for allocation to either treatment. All participants were blinded to the assignment before scratching the card, but we did not blind patients or their physicians to their assignments after randomisation because the two types of progestogen therapy were totally different in administration method. All patients underwent CL measurement at the time of randomisation. Follow-up CL measurements were performed at 20–23, 24–28, 32–34 and 36–38 weeks of gestation. Women in the PTB history group were retained in the same group even if the follow-up CL decreased to <25 mm.

Intervention

After randomisation, women in the vaginal group self-administered 200 mg of vaginal micronised natural progesterone (Utrogestan®) daily and women in the IM group received a weekly IM injection of 250 mg of 17-OHPC (Jenapharm®). Women in the IM and vaginal groups visited the hospital every 1 or 2 weeks, respectively. At every visit, a self-recorded diary card for treatment drug use was checked for both groups. Unused drugs were collected and counted for the vaginal group to assess compliance. The compliance rate was calculated by dividing the number of drugs actually administered by the total number of drugs expected to be administered. Progestogen treatment was continued until 36 weeks of gestation or until the occurrence of PTB or preterm prelabour rupture of membranes. All treatment drugs were provided by Han Wha Pharma Co., Ltd (Seoul, Korea).

Measurements

The primary outcome of this study was PTB before 37 weeks of gestation. Gestational age was estimated based on the last menstrual period, when reliable, or on ultrasonography performed during the first trimester. Secondary outcomes were gestational age at delivery, PTB before 34 and 28 weeks of gestation, maternal and neonatal morbidities, adverse events, compliance with medication and patient satisfaction. Patient satisfaction was assessed by a five-point Likert scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied and very dissatisfied) at the final visit.

Statistical analysis

Sample size calculation was performed based on an equivalence test. The hypothesis used was H0, $|P_T - P_A| \geq \delta$, versus H1, $|P_T - P_A| < \delta$, where P_T was response rate in the test group, P_A was response rate in the control group and δ was the equivalence margin. P_T and P_A were estimated to be 22.0%, which was the incidence of PTB in Korean women treated with vaginal progesterone from a previous retrospective study.[25] The calculated sample size was 266 (133 in each group) at an equivalence margin of 15%, with a two-sided α level of 0.05, β level of 0.2 and estimated dropout rate of 10%. The equivalence margin of 15% was determined based on the equivalence limits for a binary response,[26] considering an expected response rate (i.e. no PTB before 37 weeks of gestation) of 80%. This margin was regarded as the difference that can be considered clinically (smaller than the difference between progestogen and placebo treatment in previous studies) and practically (the number of subjects suitable to enrol in the study) acceptable.

The data obtained were analysed using SPSS 24 (IBM, Armonk, NY, USA). The primary outcome was analysed by the equivalence test, and the two types of progestogen therapy were considered equivalent if the 95% CI for the risk difference lies within the equivalence margin of −15% to +15%. A two-sample Student's *t*-test or Wilcoxon rank-sum test was used to compare continuous variables, as appropriate. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. Multivariable analysis was performed to adjust for stratification factors (PTB history and short CL). A generalised estimating equation was used to calculate adjusted risk differences, relative risks and their 95% CIs of PTB, and an analysis of covariance was used to compare the mean gestational age at delivery between the two groups. Results were considered statistically significant when the *P* value was <0.05.

Data were analysed according to intention-to-treat analysis, including participants who received the treatment drug at least once and were assessed for its efficacy. Per-protocol analysis was performed for participants who completed the study until the final visit without any protocol violation, such as not meeting the selection criteria, a compliance rate of <70% or termination of pregnancy before 20 weeks of gestation. We performed subgroup analyses according to indications of progestogen therapy (PTB history group, short cervix group and both PTB history and short cervix group). An interaction test was performed using the generalised estimating equation to evaluate the influence of each subgroup on the relationship between progestogen therapy and outcomes.

Meta-analysis

We performed a meta-analysis including randomised controlled trials that compared vaginal progesterone and IM 17-OHPC for the prevention of PTB in singleton pregnant women with a history of PTB or with short CL. We conducted electronic searches in PubMed, Embase, Scopus,

ClinicalTrials.gov and Google Scholar from inception until February 2020. The terms 'intramuscular', 'vaginal', 'progesterone', 'progestin', 'progestogen', 'preterm' and 'cervical length' were used to search for articles. The details of the selected studies were reviewed, and the data were combined with the data from our current study. The primary outcomes of the meta-analysis were PTB before 37, 34 and 28 weeks of gestation. The summary measures were reported as risk ratios with 95% CIs. Heterogeneity of treatment effects between studies was tested using Cochrane's Q test and heterogeneity index (I^2). Combined-effect estimates were calculated under a fixed-effects model.

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Results

From February 2015 to August 2018, 269 women were screened for eligibility. The first patient was randomised on 12 February 2015, and the last study visit was 1 January 2019. Three women were excluded and 266 women were randomly assigned to the vaginal group (n = 131) and the IM group (n = 135) (Figure 1). Nineteen women (12 in the vaginal group and seven in the IM group) were lost to follow-up after randomisation. Hence, a total of 247 women (119 and 128 women in the vaginal and IM groups, respectively) were available for the intention-to-treat analysis. Forty women were excluded for protocol violations (24 and 16 women in the vaginal and IM groups, respectively). A total of 207 women (95 and 112 women in the vaginal and IM groups, respectively) were available for the per-protocol analysis.

In the intention-to-treat analysis, the two groups had similar maternal characteristics and obstetric histories (Table 1). Risks of PTB before 37 weeks of gestation did not significantly differ between the two groups (vaginal group versus IM group, 22.7 versus 25.8%, P = 0.571; Table 2). The difference in the risk of PTB before 37 weeks of gestation between the two groups was 3.1% (95% CI −7.6 to 13.8%), which was within the equivalence margin of 15%. The difference in the risk of PTB before 37 weeks of gestation (vaginal group versus IM group, 22.2 versus 26.3%), adjusted for stratification factors (PTB history and short CL), was 4.1% (95% CI −6.3 to 14.5%), which still lay within the equivalence margin of 15%. Risks of overall PTB before 34 and 28 weeks of gestation, spontaneous PTB before 37, 34 and 28 weeks of gestation and mean gestational age at delivery were also similar between the two groups. CL progressively shortened as gestational age progressed in both groups (Table 3); however, CL values at randomisation or CL measurements at follow-up did not significantly differ between the two groups. The compliance with medication was significantly lower in the vaginal group than in the IM group (91.4 ± 16.2 versus 95.3 ± 12.9%, P = 0.037). Other secondary outcomes, including maternal and neonatal morbidities, adverse events and patient satisfaction, were similar between the two groups.

In the per-protocol analysis, maternal characteristics, obstetric history, CL at randomisation and follow-up CL measurements were similar between the two groups (Table S1). The difference in the risk of PTB before 37 weeks of gestation between the two groups was 1.7% (95% CI −13.5 to 10.2%), which was within the equivalence margin of 15% (Table S2). Other secondary outcomes were comparable between the two groups (Table S3). However, the compliance with medication was significantly lower in the vaginal group compared with the IM group (93.3 ± 13.5 versus 97.5 ± 8.6%, P = 0.001).

In the subgroup analysis according to indications of progestogen therapy (PTB history group, short cervix group and both PTB history and short cervix group), no significant difference in the risks of overall and spontaneous PTB before 37, 34 or 28 weeks of gestation or mean gestational age at delivery was noted between the vaginal group and the IM group for all subgroups (Table S4). The interaction test between the progestogen therapy and each subgroup was not significant for all outcomes. Maternal characteristics, obstetric history, CL at randomisation, follow-up CL measurements and other secondary outcomes were also similar between the vaginal and the IM group for all subgroups (data not shown).

We identified five randomised controlled trials that compared vaginal progesterone and IM progestin for the prevention of PTB in singleton pregnant women with history of PTB or short CL (Table S5).[27–31] Daily gel (90 mg) was used for vaginal progesterone in one study,[27] and daily tablets (100–400 mg) were used for vaginal progesterone in the other four studies.[28–31] The weekly administration of 250 mg 17-OHPC was used for IM progestin in all studies. The meta-analysis comprised 1367 women (687 in the vaginal and 680 in the IM group) who were enrolled in these five studies and in our current study. We performed a meta-analysis including all six studies (vaginal gel or tablet versus IM 17-OHPC) and those including only vaginal tablet versus 17-OHPC. The results showed that there were no significant differences in the risks of PTB before 37, 34 and 28 weeks of gestation between the vaginal and IM groups (Figures S1 and S2).

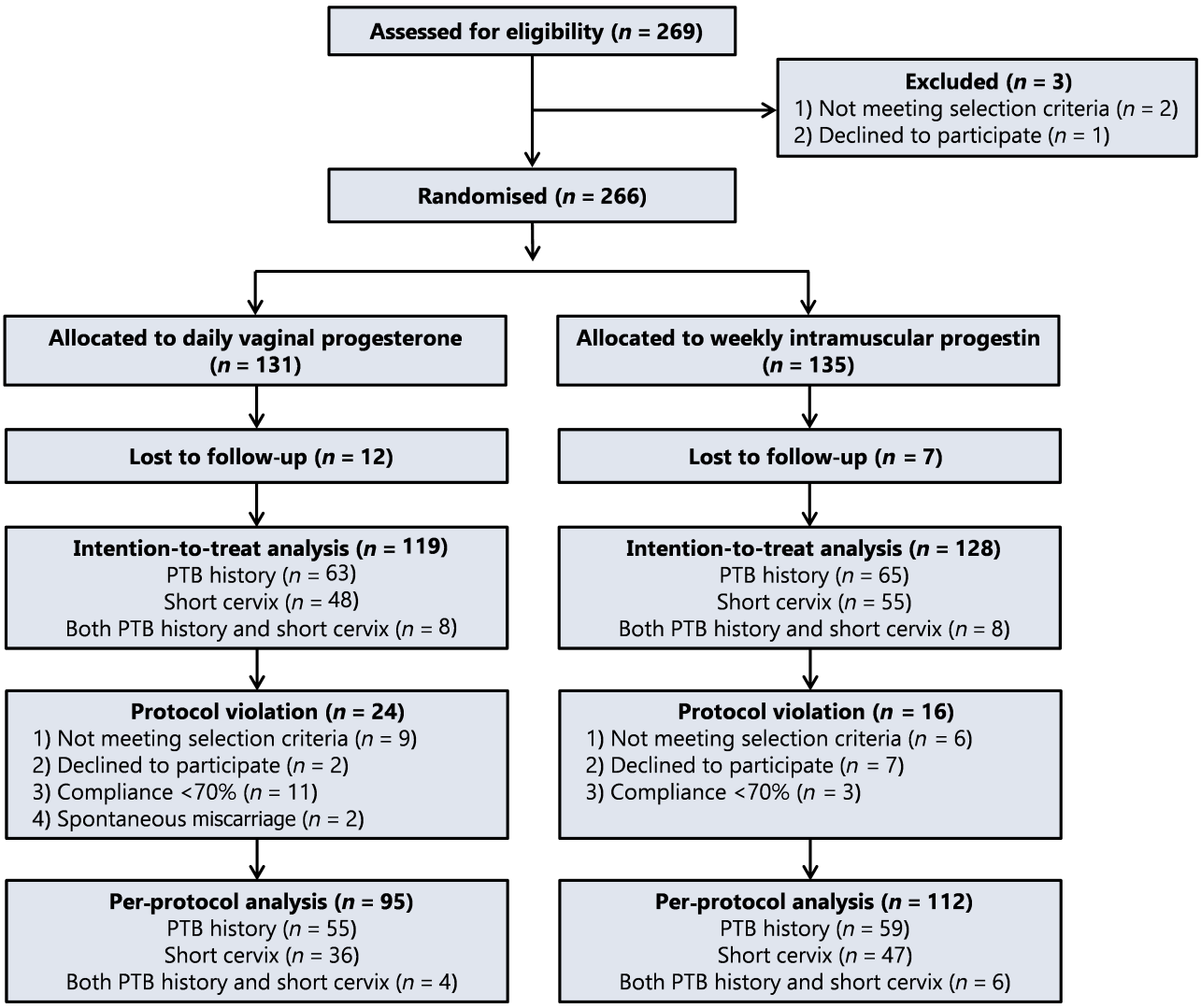

Figure 1. Flow chart showing the selection of participants.

Discussion

Main findings

This multicentre randomised trial compared the efficacy of two regimens of progestogen therapy. The results showed that treatment with a weekly IM injection of 250 mg 17-OHPC compared with daily vaginal administration of 200 mg of micronised progesterone might increase the risk of PTB before 37 weeks of gestation by as much as 13.8% or reduce it by as much as 7.7% in women with a history of spontaneous PTB and/or short CL.

Strengths and limitations

The strength of our study lies in its randomised controlled design, although this study was not double blinded. To minimise selection bias, however, participants were blinded to the assignment of the treatment drug before scratching the card.

One of the limitations of our study was its heterogeneous study population: women with a history of PTB or women with short CL. Although the risks of primary and secondary outcomes were similar between vaginal and IM progestogen therapy groups in each subgroup, the sample size of each subgroup, especially those with both risk factors, was too small to verify whether the efficacy of progestogen supplement therapy was different according to indications of treatment. Another limitation was that the method for determining the equivalence margin was classical. Therefore, an equivalence margin of 15% may be too large to have sufficient power to detect substantial differences between the two types of therapy. This study was further limited by a high number of protocol violations, by

Table 1. Maternal characteristics (intention-to-treatment analysis)

	Vaginal (n = 119)	IM (n = 128)
Age (years)	33.7 ± 3.7	33.5 ± 3.5
Weight (kg)	61.4 ± 10.8	61.1 ± 9.9
Height (cm)	161.2 ± 5.2	161.8 ± 5.3
Body mass index (kg/m^2)	23.6 ± 3.8	23.4 ± 3.7
Parous	93 (78.2%)	105 (82.0%)
History of previous PTB	71 (59.7%)	73 (57.0%)
GA at delivery in prior PTB (weeks)	30.7 ± 4.7	30.0 ± 5.4
GA at randomisation (weeks)	19.7 ± 2.3	19.4 ± 2.3
CL at randomisation (cm)	28.9 ± 9.3	28.4 ± 9.2
Stratification group		
PTB history	63 (52.9%)	65 (50.8%)
Short cervix	48 (40.3%)	55 (43.0%)
Both PTB history and short cervix	8 (6.7%)	8 (6.3%)

CL, cervical length; GA, gestational age; IM, intramuscular; PTB, preterm birth. Data are presented as mean ± standard deviation or number (%).

no blinding after randomisation and by excessively broad exclusion criteria, which might limit the generalisability. Despite these limitations, this study was meaningful in that it was the first multicentre, randomised, investigator-initiated trial in the maternal and fetal medicine field in Korea.

Interpretation

Currently, progestogen supplement therapy is recommended for women with a history of spontaneous PTB or with short CL by many guidelines, including those of the National Institute for Health and Care Excellence and the American College of Obstetricians and Gynecologists.[32–35] There is no clear consensus on the optimal indication, route of administration or dose among these guidelines, however, because the selection criteria of the study populations and methods of progestogen therapy vary substantially among the available studies.[14]

Intramuscular progestin therapy was effective in preventing PTB in women with a history of PTB in some studies,[5,17,36] but not in women with short CL.[37,38] In contrast to IM progestin therapy, vaginal progesterone therapy has been shown to be effective in preventing PTB both in women with history of spontaneous PTB and in women with short CL in many randomised trials,[19,20,22,39,40] but not in all.[23] Nevertheless, subsequent meta-analysis showed that vaginal progesterone therapy was significantly associated with a decreased risk of PTB and neonatal morbidity and mortality in women with short CL.[41] Our study results cannot reveal the beneficial effect of progestogen supplement therapy because we did not compare the results with those of placebo. We found that the efficacy of vaginal and IM progestogen therapies was equivalent in preventing PTB in women with a history of spontaneous PTB or short CL, however, consistent with previous studies (Table S5).[28–31]

When designing our study, only one randomised controlled trial compared vaginal with IM progestin therapy to prevent PTB.[27] In that study, 518 singleton pregnant women with a history of PTB were randomised to a weekly IM injection of 250 mg of 17-OHPC or to a daily vaginal administration of 90 mg of micronised progesterone gel. The vaginal progesterone gel therapy group had significantly lower risks of PTB before 34 weeks of gestation and at 28–32 weeks of gestation, and a lower risk of adverse effects. Since then, four randomised trials comparing the daily administration of a vaginal progesterone tablet and a weekly IM injection of 250 mg of 17-OHPC in singleton pregnant women with a history of PTB or short CL have been published. None of these studies found any significant difference in the risk of PTB before 37 weeks of gestation, mean gestational age at delivery or neonate outcomes between the two types of therapy, however (Table S5).[28–31]

Table 2. Primary outcome and pregnancy outcome (intention-to-treatment analysis)

	Vaginal (n = 119)	IM (n = 128)	P	aRR (95% CI)*
PTB <37 weeks	27 (22.7%)	33 (25.8%)	0.571	0.845 (0.549–1.301)
PTB <34 weeks	16 (13.4%)	11 (8.6%)	0.222	1.522 (0.741–3.126)
PTB <28 weeks	8 (6.7%)	4 (3.1%)	0.189	2.088 (0.658–6.626)
Spontaneous PTB <37 weeks	23 (19.3%)	28 (21.9%)	0.621	0.857 (0.527–1.395)
Spontaneous PTB <34 weeks	16 (13.4%)	9 (7.0%)	0.095	1.874 (0.864–4.062)
Spontaneous PTB <28 weeks	8 (6.7%)	4 (3.1%)	0.189	2.088 (0.658–6.626)
GA at delivery (weeks)*,**	37.4 (36.7, 38.1)	37.6 (37.0, 38.3)	0.619	–

aRR, adjusted relative risk; CI, confidence interval; GA, gestational age; IM, intramuscular; PTB, preterm birth. Data are presented as number (%).
*Adjusted for stratification factors (PTB history and short cervix).
**Data are presented as least-square mean (95% CI).

Table 3. Other secondary outcomes (intention-to-treatment analysis)

	Vaginal (n = 119)	IM (n = 128)	P-value
CL at 20–23 weeks of gestation (cm)	28.4 ± 9.2	27.6 ± 10.2	0.531
CL at 24–28 weeks of gestation (cm)	28.9 ± 8.7	27.5 ± 9.3	0.236
CL at 32–34 weeks of gestation (cm)	24.3 ± 9.7	23.3 ± 8.6	0.438
CL at 36–38 weeks of gestation (cm)	20.2 ± 9.7	18.8 ± 9.3	0.354
Compliance (%)	91.4 ± 16.2	95.3 ± 12.9	0.037
Gestational diabetes*	12 (10.7%)	10 (8.1%)	0.497
Emergency cerclage	12 (10.1%)	16 (12.5%)	0.550
Admission for preterm labor	32 (26.9%)	47 (36.7%)	0.098
Maternal adverse events	1 (0.8%)	2 (1.6%)	0.605
Maternal composite morbidity**	2 (1.7%)	6 (4.7%)	0.284
Caesarean section	47 (39.5%)	54 (42.2%)	0.667
Birthweight (kg)	2.98 ± 0.80	2.92 ± 0.68	0.528
1-minute Apgar score of <4	5 (4.3%)	5 (3.9%)	>0.009
5-minute Apgar score of <7	6 (5.1%)	5 (3.9%)	0.645
Neonatal composite morbidity***	18 (15.4%)	18 (14.1%)	0.770
Sex (male)	62 (52.5%)	68 (53.1%)	0.927
Likert scale******			
Very satisfied	49 (50.0%)	59 (57.8%)	0.586
Satisfied	38 (39.8%)	33 (32.4%)	
Neither satisfied nor dissatisfied	6 (6.1%)	8 (7.8%)	
Dissatisfied	3 (3.1%)	2 (2.0%)	
Very dissatisfied	1 (1.0%)	0 (0%)	

CL, cervical length; IM, intramuscular; RDS, respiratory distress syndrome. Data are presented as mean ± standard deviation or number (%).
*Data unavailable for seven and five women in the vaginal group and the IM group, respectively, who delivered before gestational diabetes screening.
**Defined as having more than one of the following: death, intensive care unit admission, postpartum haemorrhage, pulmonary embolism, seizure, infection, genital laceration, neuropathy and surgical complications.
***Defined as having more than one of the following: death, RDS, necrotising enterocolitis, brain injury, retinopathy of prematurity, anaemia, jaundice, infection and neonatal intensive care unit admission.
****Data unavailable for 21 and 26 women in the vaginal group and the IM group, respectively.

To assess our findings in the context of other studies we undertook a meta-analysis of six randomised trials, including our study (Figures S1 and S2). The results showed that there were no significant differences in the risks of PTB before 37, 34 and 28 weeks of gestation between the vaginal (tablet or gel) and IM progestogen treatments. This result differs from recent meta-analyses,[42,43] which favoured vaginal progesterone as a gel or tablet (with lower risks of PTB before 34 and 32 weeks of gestation, but with similar risks of PTB before 37 and 28 weeks of gestation) compared with women who received 17-OHPC. These meta-analyses included just three studies, however, and 72% of women were from a single study that showed a favourable outcome using vaginal progesterone gel.

When the efficacy of two regimens of progestogen therapy in preventing PTB is similar, the treatment of choice may depend on the cost, adverse effects and satisfaction of patients. Regarding the adverse effects of drugs, adverse events occurred in about 1% of the women, although the rates did not significantly differ between the two groups. We hypothesised that women might prefer vaginal therapy because IM injection is less convenient in terms of being more painful and requiring more frequent hospital visits. Patient satisfaction did not significantly differ between the two groups, however, and nearly 90% of women reported that they were satisfied or very satisfied with the treatments.

An intriguing finding of our study was that the compliance rate was substantially high: more than 95% overall. The high compliance rate can be explained by the fact that the women participating in this study might have been highly motivated because they are very concerned about PTB, especially those with a history of PTB. The compliance rate was significantly lower in the vaginal group than in the IM group, however. This suggests that daily vaginal administration might be more easily neglected than weekly visits to the hospital for IM injection. The difference in the follow-up frequencies of the two groups might have an effect on the compliance rate. Despite the differences in follow-up frequencies and compliance rates of the two groups, the risk of PTB did not significantly differ between the two groups, however.

Conclusion

In conclusion, this multicentre, randomised, open-label, equivalence trial showed that treatment with weekly IM progestin compared with daily vaginal progesterone might increase risk of PTB before 37 weeks of gestation by as much as 13.8%, or reduce it by as much as 7.6%, in women with history of spontaneous PTB or short CL.

Disclosure of interests

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Healthcare and non-financial support from Han Wha Pharma Co., Ltd, during the conduct of the study. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

S-JC and YJK conceived the study, S-JC, SML, SKC and YJK designed the study and S-JC, DWK, KK, S-CK, J-YK, YHK, SN, J-GB, H-HC, J-YS, KYO, KAL, SMK, IAC, SML, GJC, YSJ, GYC, SKC, SEH, HSH and YJK performed the study. S-JC and YJK analysed the data and wrote the article.

Details of ethics approval

This study was approved by the Ministry of Food and Drug Safety of Korea (approvalno. 30062) on 23 January 2014, and by the Institutional Review Board of each participating centre.

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Clinical trial registration

This trial was registered at ClinicalTrials.gov on 26 November 2014; date of initial participant enrolment was 11 February 2015; clinical trial identification number is NCT02304237 (https://clinicaltrials.gov/ct2/show/NCT02304237).

Presentation at the meeting

This study was presented at the 25th Annual Meeting of the Korean Society for Maternal–Fetal Medicine, Jejudo, South Korea, 8 June 2019.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Forest plot for risk of PTB, randomised to vaginal (tablet or gel) or intramuscular progestogen.

Figure S2. Forest plot for risk of PTB, randomised to vaginal (tablet) or intramuscular progestogen.

Table S1. Maternal characteristics (per-protocol analysis).

Table S2. Primary outcome and pregnancy outcome (per-protocol analysis).

Table S3. Other secondary outcomes (per-protocol analysis).

Table S4. Primary outcome and pregnancy outcome of subgroups.

Table S5. Summary of randomised trials of vaginal versus IM progestogen therapy for the prevention of PTB. ■

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