# *EFFECT OF PROGESTERONE ON LATENT PHASE PROLONGATION IN PATIENTS WITH PRETERM PREMATURE RUPTURE OF MEMBRANES*

**KARYA ILMIAH AKHIR NERS**

**Untuk Memenuhi Salah Satu Persyaratan dalam Menyelesaikan Program Pendidikan Profesi Ners**

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## LEMBAR PERSETUJUAN

Yang bertanda tangan di bawah ini menyatakan bahwa

Karya Ilmiah Akhir Ners yang berjudul *Effect Of Progesterone On Latent Phase Prolongation In Patients With Preterm Premature Rupture Of Membranes* telah melakukan proses bimbingan dan dinyatakan layak untuk diseminarkan didepan dewan penguji.

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**LEMBAR PENGESAHAN**

Yang bertanda tangan di bawah ini menyatakan bahwa

Karya Ilmiah Akhir Ners yang berjudul "*Effect Of Progesterone On Latent Phase Prolongation In Patients With Preterm Premature Rupture Of Membranes*" telah dilakukan seminar / sidang yang dihadiri oleh audiens dan dewan penguji.

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# KATA PENGANTAR

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Penulis menyadari bahwa laporan ini masih jauh dari sempurna. Oleh karenanya, diharapkan saran dan kritik yang membangun agar penulis dapat menjadi lebih baik lagi di masa mendatang.

Semoga laporan kegiatan ini menambah wawasan dan memberi manfaat bagi pembaca.

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Penulis

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# *EFFECT OF PROGESTERONE ON LATENT PHASE PROLONGATION IN PATIENTS WITH PRETERM PREMATURE RUPTURE OF MEMBRANES*

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## ABSTRAK

Latar belakang : Ketuban pecah dini (PPROM) adalah suatu kondisi yang menyebabkan peningkatan resiko morbiditas dan mortalitas ibu dan bayi pada ibu hamil. Untuk mencegah komplikasi ini, beberapa penelitian mengusulkan untuk penggunaan terapi progesterone profilaksis.
Skenario kasus : pasien dating dengan usia kehamilan 30 minggu ke RS X dengan keluhan keluar air dari jalan lahir, tekanan darah 120/80 mmHg, TFU 30 cm DJJ 140x/menit his belum ada. Saat diperiksa menggunakan kertas lakmus merah berubah menjadi biru, selaput ketuban tidak teraba. Pemeriksaan hematologi didapatkan hasil Hb 10 g/dL, leukosit 13.530 $mm^3$ , protein urin (-).
Strategi penelusuran bukti : Penulis melakukan pencarian artikel dari database PubMed dan Google Scholer. Pada pencarian, didapatkan 2 artikel yang sesuai dengan kriteria yang diinginkan dan dilakukan telaah kritis terhadap artikel-artikel tersebut.
Kesimpulan : Berdasarkan pembahasan dari jurnal yang telah dikumpulkan, salah satu terapi yang dapat diberikan untuk memperpanjang fase laten dan meminimalkan resiko ketuban pecah dini adalah pemberian progesteron.
Kata kunci : Fase laten, Ketuban Pecah Dini, PPROM, Progesteron

*Nursing Professional Study Program*

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## *ABSTRACK*

*Background : Premature rupture of membranes (PPROM) is a condition that causes an increased risk of maternal and infant morbidity and mortality in pregnant women. To prevent this complication, several studies have suggested the use of prophylactic progesterone therapy.*
*Case scenario: a patient comes with a gestational age of 30 weeks to RS X with complaints of discharge from the birth canal, blood pressure 120/80 mmHg, TFU 30 cm FHR 140x/minute his is not present. When examined using red litmus paper turns blue, the amniotic membranes are not palpable. Hematological examination showed Hb 10 g/dL, leukocytes 13,530 mm3, urine protein (-).*
*Evidence search strategy: The author conducted a search for articles from the PubMed and Google Schler databases. In the search, 2 articles were found that matched the desired criteria and a critical study was carried out on these articles.*
*Conclusion : Based on the discussion from the journals that have been collected, one of the therapies that can be given to prolong the latent phase and minimize the risk of premature rupture of membranes is the administration of progesterone.*
*Key words : Latent phase, Premature rupture of membranes, PPROM, Progesterone*

## A. PENDAHULUAN

Ketuban pecah dini (KPD) atau *Premature Rupture of the Membranes* (PROM) adalah keadaan pecahnya selaput ketuban sebelum terjadinya proses persalinan pada kehamilan aterm. Sedangkan *Preterm Premature Rupture of the Membranes* (PPROM) adalah pecahnya ketuban pada pasien dengan usia kehamilan kurang dari 37 minggu (Parry and Strauss, 1998; Brian and Mercer, 2003; Mamede dkk., 2012). Pendapat lain menyatakan dalam ukuran pembukaan servik pada kala I, yaitu bila ketuban pecah sebelum pembukaan pada primigravida kurang dari 3 cm dan pada multigravida kurang dari 5 cm. Dalam keadaan normal selaput ketuban pecah dalam proses persalinan (Cunningham, 2010; Soewarto, 2010).

Kejadian ketuban pecah dini (KPD) terjadi pada 10 - 12% dari semua kehamilan. Pada kehamilan aterm insidensinya 6 -1 9%, sedangkan pada kehamilan preterm 2 - 5%. Laporan lain mendapatkan ketuban pecah dini terjadi pada sekitar 6 - 8% wanita sebelum usia kehamilan 37 minggu dan secara langsung mendahului 20 - 50% dari semua kelahiran prematur (Getahun dkk., 2012). Insiden KPD di seluruh dunia bervariasi antara 5 - 10% dan hampir 80% terjadi pada usia kehamilan aterm (Adeniji dkk., 2013; Endale dkk., 2016).

Sementara itu, insiden KPD preterm diperkirakan sebesar 3 - 8% (Okeke dkk., 2014). Dalam keadaan normal, 8 - 10% wanita hamil aterm akan mengalami KPD dan hanya 1% terjadi pada usia kehamilan preterm (Soewarto, 2010). Prevalensi dari

KPD preterm di dunia adalah 3 - 4,5 % kehamilan (Lee, 2011) dan merupakan penyumbang dari 6 - 40 % persalinan preterm atau prematuritas (Furman dkk., 2010). Di China dilaporkan insiden KPD lebih tinggi sekitar 19,53% dari seluruh kehamilan (Yu, 2015), sedangkan di Indonesia berkisar antara 4,5 - 7,6% (Wiradarma dkk., 2013). Kejadian persalinan dengan KPD pada usia kehamilan aterm (≥37minggu) yaitu 179 kasus (84,43%), sedangkan pada preterm sebanyak 33 kasus (15,57%).

Ketuban pecah dini berhubungan dengan penyulit kelahiran prematur dan terjadinya infeksi korioamnionitis yang dapat meningkatkan angka morbiditas dan mortalitas perinatal. Salah satu penyebab utama kelahiran prematur adalah ketuban pecah dini prematur (PPROM) yang terjadi pada 3% dari semua kehamilan. Kelahiran prematur adalah salah satu faktor risiko terpenting untuk morbiditas dan mortalitas di masa depan di antara neonatus yang mencakup hingga 85% morbiditas dan mortalitas prenatal . peningkatan fase laten pada konteks PPROM akan mengakibatkan komplikasi yang dapat membahayakan ibu dan anak, yaitu terjadinya infeksi. Morbiditas dari PPROM akan berdampak pada organ dan sistem vital tubuh, termasuk paru-paru, sistem gastrointestinal, jantung dan sistem saraf pusat dan resiko lebih tinggi terjadi pada bayi baru lahir prematur. Morbiditas yang terjadi pada ibu melahirkan juga mengalami peningkatan komplikasi yang muncul seperti korioamnionitis dan sepsis yang membahayakan. Intervensi yang diberikan pada ketuban pecah dini antara lain dengan penggunaan antibiotik, kortikosteroid, tokolitik, serviks cerclage dan terutama progesteron. Progesteron adalah hormon seks

yang memiliki banyak peran yang dipahami dengan baik dalam kehamilan normal, salah satunya adalah efek antiinflamasi yang melawan kerja sitokin inflamasi yang diproduksi secara rutin selama kelahiran, yang memicu persalinan prematur. Dengan demikian progesteron secara teoritis dapat memiliki efek positif dalam mencegah kelahiran prematur.

## B. SKENARIO KLINIS

Pasien Ny.X datang dengan keluhan keluar air dari jalan lahir usia kehamilan 30 minggu belum disertai mulas. Pada data obyektif didapatkan hasil keadaan umum ibu baik tekanan darah 120/80 mmHg, TFU 30 cm DJJ 140x/menit his belum ada. Di genetalia dan vulva vagina tidak ada kelainan, gerakan janin dirasakan aktif lebih dari 10 kali selama 12 jam, terdapat pengeluaran cairan dari jalan lahir ibu berwarna jernih. Saat diperiksa menggunakan kertas lakmus merah berubah menjadi biru, selaput ketuban tidak teraba. Pemeriksaan hematologi didapatkan hasil Hb 10 g/dL, leukosit 13.530 $mm^3$ , protein urin (-). Diagnose keperawatan yang ditegakkan pada laporan kasus ini adalah Ny.X 37 tahun G4P3A0 usia kehamilan 30 minggu dengan Ketuban Pecah Dini. Janin tunggal hidup intrauterine. Berdasarkan diagnose tersebut maka penatalaksanaan yang dilakukan adalah lakukan kolaborasi dengan dokter dengan advice pemberian induksi persalinan, infuse glukosa 5% 500 ml 20 tpm drip oksitosin 5 iu, injeksi cefotaxime 1 gr, memberikan dukungan psikologi pada ibu untuk menghadapi persalinan serta melakukan observasi kemajuan persalinan dan

memantau kesejahteraan janin. Pada penatalaksanaan akhir advice dokter persalinan dilakukan secara section caesaria dengan indikasi gagal induksi.

Pada kala 1 (pembukaan jalan lahir) dimulai dengan kontraksi uterus yang teratur dan diakhiri dengan dilatasi serviks lengkap. Proses membukanya serviks sebagai akibat his dibagi dalam 2 fase yaitu fase laten dan fase aktif. Dimana pada fase laten berlangsung selama 8 jam yang ditandai dengan penurunan hormone progesterone.

## C. RUMUSAN MASALAH

Berdasarkan latar belakang diatas dapat dirumuskan bahwa ketuban pecah dini adalah pecahnya selaput ketuban sebelum proses persalinan. Sehingga diperlukan pemberian terapi yang dapat mempertahankan ketuban yaitu dengan pemberian progesterone untuk mengurangi kontraksi uterus pada usia preterm. Sehingga kami tertarik untuk meneliti bagaimana efek dari pemberian progesteron pada fase laten pasien dengan ketuban pecah dini ?

## D. STRATEGI PENCARIAN

Penelusuran jurnal dilakukan dengan menggunakan PubMed *Advanced Search Builder* pada tanggal 23 Mei 2021 dengan menggunakan kata kunci yang tercantum dalam tabel 1. Untuk mempersempit hasil yang telah didapatkan dilakukan

seleksi dengan menetapkan kriteria inklusi dan eksklusi yang telah ditentukan sebelumnya. Rincian tentang pencarian jurnal tersebut tercantum pada tabel 1 dan gambar 1.

**Tabel 1.** Strategi Pencarian Jurnal di PubMed *Advanced Search Builder* tanggal 23 Mei 2021

| Database | Strategi Pencarian | Jumlah Artikel Yang Ditemukan | Artikel Yang Dipilih |
|---|---|---|---|
| PubMed (23 Mei 2021) | *Preterm premature rupture of membrans and hispatologis and leukositosis* | 15 | 1 |
| Google Scholar (13 Agustus 2021) | *Preterm premature rupture of membrans and hispatologis and leukositosis* | 6 | 1 |

| Nama Penulis & Tahun | Tujuan dan Pertanyaan penelitian | Desain Penelitian | Besar Sampel | Variabel Penelitian | Uji Statistik | Hasil Penelitian | Kekuatan Penelitian | Kelemahan Penelitian | Kesimpulan Untuk Praktek Keperawatan |
|---|---|---|---|---|---|---|---|---|---|
| Abdali, et al (2017) | Penelitian ini dilakukan untuk mengetahui pengaruh progesterone pada fase laten ibu dengan PPROM | *Randomized control triall* | 120 responden | Variabel terikat : pemberian progesterone Variabel bebas: pemberian plasebo | Uji independent sample T-test dan uji chi-square | Fase laten median adalah 8,5 hari pada kelompok intervensi vs. 5 hari pada kelompok kontrol dalam 28 hari-30minggu kehamilan, yang secara signifikan lebih tinggi pada kelompok intervensi(P= 0,001). Di antara variabel hasil ibu dan bayi, hanya rata-rata berat | Dalam jurnal sudah didukung oleh beberapa penelitian lain yang menjelaskan pemberian terapi dengan berbagai dosis berbeda | Kelemahan pada penelitian ini tidak menyampaikan hasil keektifan dari perbedaan dosis progesteron yang diberikan | Pemberian terapi progesterone mampu mengurangi kontraksi uterus yang akan mengakibatkan terjadinya ketuban pecah dini |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | badan lahir yang secara signifikan lebih tinggi pada kelompok intervensi dibandingkan pada kelompok kontrol(1609, 92 ± 417,28 gr vs 1452,03±342, 35gr,P=0,03). | | | |
| Joan, et al (2020) | Penelitian ini dilakukan untuk mengetahui pengaruh progesterone pada ibu dengan HIV | *Randomized control triall* | 140 responden | Variabel terikat : pemberian progesterone<br>Variabel bebas: pemberian plasebo | Uji regresi poissom | Nilai rata-rata adalah 94% (SD±9,4); 91% (n = 125/137) mencapai kepatuhan keseluruhan 80%. Hasil pengiriman dipastikan dari 134(96%) peserta. PTB | Dalam penelitian ini menggunakan responden yang banyak serta pengukuran yang lebih lengkap | Kelemahan dalam penelitian ini yaitu tidak adanya pembahasan mengenai perbedaan cara pemberian progesteron | Pemberian terapi progesterone mampu meningkatkan usia kehamilan PPROM |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | spontan terjadi pada 10 peserta(15%) yang menerima plasebo dan 8(12%) yang menerima progesteron (RR 0,82;95%CI: 0,34-1,97). PTB spontan < 34 minggu terjadi pada 6(9%) menerima plasebo dan 4(6%)menerima progesteron( RR 0,67; 95% CI: 0,20-2,67). | | | |

**Tabel 2 pembahasan laporan EBCR**

## E. PEMBAHASAN

Pada penelitian Abdali (2017) mengatakan bahwa pengaruh dari pemberian progesterone pada penundaan persalinan setelah PPROM dievaluasi. Pada pemberian intervensi ini mengalami pengaruh yang signifikan menunda periode ini dari rata-rata 5 hari menjadi 8 pada kelompok intervensi berada di usia 28- 30 minggu kehamilan. Peningkatan juga terjadi secara signifikan pada berat lahir neonatus. Norman dkk., melakukan uji klinis acak untuk menyelidiki efek progesteron pada profilaksis persalinan prematur di PPROM dan menemukan bahwa tidak ada peningkatan yang signifikan dalam periode waktu antara PPROM dan persalinan pada kelompok intervensi. Mereka juga menyimpulkan bahwa progesteron tidak meningkatkan morbiditas atau mortalitas pada ibu atau anak. Hasil penelitian ini tidak sesuai dengan penelitian ini, karena perbedaan tersebut diduga disebabkan oleh fakta bahwa dosis progesteron yang lebih rendah digunakan oleh mereka (200 dibandingkan dengan 400 mg).

Menurut Meis (2017) yang melakukan penelitian kepada 459 responden dengan riwayat persalinan premature membagi 2 kelompok intervensi dan kelompok control. Pada kelompok intervensi diberikan injeksi progesteron intramuskular 250 mg/minggua dan plasebo pada kelompok lain. Angka terjadinya persalinan prematur secara signifikan lebih rendah terjadi pada pasien yang diberi progesteron. Komplikasi neonatal seperti perdarahan intraventrikular dan enterokolitis nekrotikans juga lebih rendah pada kelompok intervensi. Pada pemberian terapi progesterone tidak ditemukan adanya efek samping yang dilaporkan. Meskipun komplikasi neonatal seperti sepsis, sindrom gangguan pernapasan tidak berkurang secara signifikan pada penelitian ini.

Sedangkan pada penelitian yang dilakukan oleh Defonseca (2019) kepada 142 responden dengan PPROM diberikan progesteron dengan dosis 100 mg supositoria/hari dengan plasebo. Tingkat kelahiran prematur berkurang secara signifikan ketika mereka menggunakan progesteron. Hal ini sesuai

dengan penelitian ini menggunakan dosis yang lebih kecil dan cara pemberian yang sama. Maher (2017) melakukan uji klinis acak untuk membandingkan efektivitas supositoria intra-otot dengan vagina dan menemukan bahwa dengan dosis yang lebih rendah metode vagina secara signifikan lebih unggul. Selain itu efek samping hampir dua kali lebih tinggi pada kelompok intramuskular dibandingkan dengan kelompok vagina (14,1% vs 7,5%).

Menurut Elena (2020) yang melakukan penelitian tentang efek terapi progesterone terhadap keadaan psikologis dan kelahiran premature mengatakan bahwa pemberian terapi progesterone sangat berpengaruh terhadap penurunan angka PPROM. Dimana status psikologis individu seorang wanita hamil merupakan faktor risiko penting dalam persalinan prematur yang akan segera terjadi. Progesterone mempengaruhi emosi positif dan optimisme yang akan berdampak pada lamanya kehamilan. Pada penelitian ini terjadi penurunan signifikan dalam optimisme dan peningkatan gejala depresi dan kecemasan diamati delapan minggu sebelum persalinan prematur (risiko relatif RR adalah 1,5), sedangkan pada wanita dengan persalinan aterm, tidak ada kejadian seperti itu yang terdeteksi.

Pada artikel yang kedua yaitu penitian oleh Price (2020) menjelaskan bahwa dari 134 peserta acak dengan data pengiriman yang tersedia, 19 (14%) melahirkan sebelum usia 37 minggu, dan 11 (8,2%) dari mereka melahirkan sebelum 34 minggu. 10 dari 67 (15%) wanita yang menerima plasebo dan 8 dari 67 (12%) darimereka yang menerima progesteron melahirkan secara spontan sebelum usia 37 minggu kehamilan (RR 0,80; 95% CI 0,33-1,91). Persalinan spontan sebelum usia kehamilan 34 minggu terjadi pada 6 dari 67 (9,0%) wanita yang menerima plasebo dibandingkan dengan 4 dari 67 (6,0%) yang menerima progesteron (RR 0,67; 95% CI 0,20-2,27). Lahir mati terjadi pada 4 dari 134 (3,0%) kehamilan, 2 menerima plasebodan 2 menerima progesteron. Berdasarkan hasil uraian

tersebut dapat disimpulkan bahwa pemberian progesterone akan menurunkan resiko kelahiran premature.

## F. KESIMPULAN

Berdasarkan hasil analisa dari kedua artikel diatas menunjukkan bahwa pemberian progesterone supositori mampu mengurangi fase laten kehamilan dan meningkatkan usia rata-rata kelahiran secara signifikan, tanpa menimbulan perubahan signifikan pada komplikasi lain. Dengan demikian progesteron sangat direcomendasikan untuk diberikan kepada wanita dengan PPROM khususnya antara usia 28-30 minggu kehamilan. Batasan dari karya ilmiah ini adalah kurangnya sumber artikel yang beragam dengan variabel yang sama bisa menjadi referensi untuk penelitian selanjutnya supaya meneliti lebih lanjut mengenai efek progesterone dan menambah jumlah artikel pendukung.

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**LAMPIRAN 1**

**(JURNAL 1)**

ORIGINAL ARTICLE

# Effect of Progesterone on Latent Phase Prolongation in Patients With Preterm Premature Rupture of Membranes

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**Abstract**- Preterm premature rupture of membranes (PPROM) is a condition leading to an increased risk of maternal and neonatal morbidity and mortality in pregnant women. To prevent this complication, some studies have proposed using prophylactic progesterone. However, due to lack of sufficient relevant data, there is still need for further studies in this regard. This study was performed to determine the effect of rectal progesterone on the latent phase and

maternal and neonatal outcome variables in females with PPROM. During the present randomized clinical trial study (IRCT201512077676N4), a total of 120 patients with PPROM at pregnancy ages between 26 and 32 weeks were randomly assigned to 2 equal intervention and control groups. In the intervention group, progesterone suppositories (400 mg per night) were administered until delivery or completion of the 34th gestational week and was compared with placebo effect in control group. The latent phase and maternal and neonatal outcome variables were compared between the two groups. The mean age of patients was 29.56±5.66 (19-42) and 29.88±5.57 (17-40) years in the intervention and control group, respectively. The two groups were almost identical in the confounding factors. The median latent phase was

8.5 days in the intervention group vs. 5 days in the control group in the $28^{th}$-$30^{th}$ weeks of gestation, which was significantly higher in the intervention group (*P*=0.001). Among maternal and neonatal outcome variables, only the mean birth-weight was significantly higher in the intervention group than that in the controls (1609.92±417.28 gr vs. 1452.03±342.35 gr, *P*=0.03). Administration of progesterone suppository in patients with PPROM at gestational ages of 28 to 30 weeks is effective in elongating the latent phase and increasing birth-weight with no significant complications.



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**Keywords:** Preterm premature rupture of membranes; PPROM; Progesterone; Latent phase

## Introduction

Preterm delivery is defined as the delivery before the end of the $37^{th}$ week of gestation and is possibly the single most important health related issue in pregnancy. One of the main etiologies for premature birth is Preterm

premature rupture of membranes (PPROM) which occurs in 3% of all pregnancies (1,2). Preterm delivery is one of the most important risk factors for future morbidity and mortality among the neonates comprising up to 85% of prenatal morbidity and mortality (3). An increased latent phase in the context of PPROM is also linked to complications, which can be harmful to the mother and the child, the most common being infections (4-6). Morbidities can arise from PPROM involving the vital organs and systems of the body, including the lungs, the gastrointestinal system, the heart and the central nervous system are drastically higher in preterm newborns (7-9). Morbidity is also higher in the birth giving mother, complications such as chorioamnionitis and sepsis being the most fearsome (10). The economic burden was as much as 26.2 billion dollars in the united states alone (11). Also premature birth causes dramatic decrease in quality of life of the parents notably the mother (12). It is thus

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obvious that preventing premature birth can have vast beneficence in many aspects. Identification of the patients in risk of preterm delivery has enhanced in recent years because of new techniques such as transvaginal cervical length measurements and fibronectin testing (13-16), but therapeutic measures have not been satisfactory in delaying birth. Regarding PPROM, many therapeutic measures have been introduced including the use of antibiotics, corticosteroids (17), tocolytics (18), cervical cerclage (19) and most notably progesterone (20,21). Alike the general trend in premature birth, previous methods regarding PPROM have also largely been unsuccessful, but progesterone has shown great promise, as a safe medication, not having any major clinical complications during pregnancy and afterwards (22). Progesterone is a sex hormone having many well understood roles in the normal pregnancies, one being the anti-inflammatory effect which counters acts against the inflammatory cytokine produced routinely during birth, which precipitates preterm delivery. Thus progesterone theoretically could have a positive effect in preventing premature birth (23). But there is contradicting evidence whether progesterone suppositories should be used in clinical contexts (20,24), and there are debates about the proper route of administration and on the most efficient dosage (3).

The present study aims to investigate the effect of progesterone on patients with PPROM and the possible change in the premature delivery rates and other pregnancy outcomes and complications regarding its use.

## Materials and Methods

During the present double blind randomized controlled trial, which was conducted in Educational- Medical centers of Tabriz University of Medical Sciences (Tabriz, Iran) between February 2014 to April 2016, 120 patients with PPROM were included in the study.

### Ethical considerations

This study was registered at Iranian Registry of Clinical Trials (http://www.irct.ir) with the registration number of IRCT201512077676N4 and the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences which was in compliance with Helsinki Declaration. All patients signed informed written consent before inclusion in the study. Before every stage of the research project, patients were clearly informed of the procedures and had the ability to leave the study at will. No harm resulting from the procedures was reported in the literature.

**Study design and population**

Inclusion criteria consisted of singleton pregnancy, PPROM (based on the agreed definition of the rapture of membranes prior to the 37th week of gestation) (25,26) between the 26-32 weeks of gestation and desire of the mother to participate in the study. Exclusion criteria were proven fetal anomalies in previous tests, including genetic testing and structural abnormalities discovered with sonography or trisomy screening tests (double marker or Quad Screen Test) between the 18-20 and 28- 32 weeks of gestation, multiple gestation, pregnancies being complicated with preeclampsia, chronic Hypertension, overt diabetes, gestational diabetes, abruption, cord prolapse and chorioamnionitis and a gestational age of more than 32 weeks in the initial presentation. This exclusion criterion was implemented because of the fact that treatment would fail to be effective in such a short time. Patients presenting more than 36 hours after the rapture of the membranes and patients with Active PPROM were also excluded.

**Randomizing, blinding and masking**

Randomizing was done in the initial presentation by the block randomization method using Randlist software (version 1.2) into two equal groups, so factors such as educational status, occupation (whether the patient was a housewife or not), residence (urban or rural), and socioeconomic levels (determined by income), previous parities, previous miscarriages, number of alive children, previous preterm deliveries and gestational age were parallel to each other. Allocation concealment was achieved by use of a placebo, which appeared identical to the active drug in every aspect and was made of Castor Oil which is proven to be safe and does not contain any therapeutic effect (27). Participants, clinicians, pharmacists, and all counterparts involved in performing the intervention, assessing results, or analyzing data remained masked to treatment allocation until the end of the study (Pharmacists were only aware of the composition of the medication given to the patients and were not aware of the allocation).

**Study protocol**

PPROM was proven by vaginal examination and observing the leakage of amniotic fluid by a single team of physicians and the placental alpha microglobuline-1 (PAMG-1) test using AmniSure ROM Test (28). Sonography was performed, and the Amniotic fluid index was measured by the same single group of radiologists, then gestational age was documented according to the first-trimester sonography. In the intervention group, 400

mg progesterone suppositories (CYCLOGEST 400 mg-
L.D. COLLINS and CO) were used once a day at night. Suppositories were continued up to delivery or to 34 completed weeks. In the control group placebo suppositories (Castor Oil), exactly in the same shape and color of the progesterone suppositories were used. All patients with PPROM were admitted to the high-risk ward and received antibiotics and betamethasone during the course of the study. Tocolytics were not used. Evaluation for chorioamnionitis and Fetal Non-Stress Test (NST) was performed daily and biophysical profile (BPP) bi-weekly. Finally, the outcome of pregnancy was examined in the following criteria: duration of latent phase (the first step of labor before the cervix dilates), from admission to delivery, route of delivery, wound infection, APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration), fetal weight at delivery, admission to NICU (neonatal intensive care unit), neonatal sepsis, the occurrence of chorioamnionitis, and puerperal metritis.

**Statistical analysis**

Statistical analysis was performed by Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, USA). Quantitative data were presented as the mean±standard deviation (SD), while qualitative data were demonstrated as frequency and percent (%). for statistical analysis, after determining the distribution of continuous variables by Kolmogorov-Smirnov test, Independent sample t-test was applied to compare two group's results. Also, collected data were studied using descriptive statistical methods, the mean difference test for independent groups, Chi Square2 test or Fisher’s exact test. *P* less than 0.05 was statistically considered

significant in all steps. Power of the study was 80%.

## Results

Patients were identical in age, education, socioeconomic status. There were no significant differences in any of the fields. Data are summarized in Table 1. Number of previous parities, number of previous miscarriages, number of live births, history of previous preterm delivery, gestational age and the time the rapture of membranes happened is depicted in Table 2. There wasn't any significant difference between any of the aforementioned.

The outcome of pregnancy was evaluated in both groups as the average amniotic fluid index, the average time from PPROM to the initial contractions, route of delivery (vaginal or cesarean), wound infection, APGAR score in the first and fifth minutes after birth, neonate blood PH, average birth weight, neonatal sepsis,respiratory distress syndrome (RDS) and days of admission in NICU. There were no significant differences between the two groups in any of the criteria except in the time from PPROM to the initial contractions when the rapture happened in the $28^{th}$-$30^{th}$ week of gestation, in which the time period was 8.5 days in the intervention group and 5 days in the control group ($P<0.001$), and the average birth weight which was 1609.92±417.28 gr in the intervention group and 1452.03+-342.35 gr in the control group ($P=0.03$). Results are summarized in Table 3. Also, there was no case of chorioamnionitis, puerperal infection, neonatal seizure, and necrotizing enterocolitis in two groups.

**Table 1. Socioeconomic state of the patients being included in the study and the comparison between the intervention and control group**

| **Groups** | | | | |
|---|---|---|---|---|
| **Social determinants** | | **Intervention** | **Control** | ***P*** |
| **Education** | **Did not graduate high school** | 28 (46.7) | 25 (41.6) | 0.93 |
| | **High school degree** | 17 (28.3) | 16 (26.7) | |
| | **College degree** | 15 (25) | 19 (3.7) | |
| **Occupation** | **House keeper** | 35 (58.3) | 36 (60) | 0.85 |
| | **Occupied** | 25 (41.7) | 24 (40) | |
| **Residence** | **Urban** | 48 (80) | 45 | 0.51 |

| | | | | |
|---|---|---|---|---|
| | **Rural** | 12 (20) | (75)<br>15 | |
| **Income($)** | **≤300** | 19 (31.7) | (25)<br>20 | |
| | **300 < <1000 $** | 36 (60) | (33.3)<br>38 | 0.5<br>1 |
| | **1000 $≥** | 5 (8.3) | (63.3)<br>2 (3.3) | |

*Data are shown as frequency (percentage)

**Table 2. Criteria matched in the control and intervention groups**

| Groups / Criteria | Intervention | Control | *P* |
|---|---|---|---|
| **Age of mother (Year)** | 29.56 ± 5.66 (19-42) | 29.88 ± 5.57 (17-40) | 0.76 |
| **Number of Previous parities** | 2.18 ± 1.11 (1-5) | 2.03 ± 1.23 (1-6) | 0.49 |
| **number of previous miscarriages** | 0.43 ± 0.08 (0-2) | 0.48 ± 0.12 | 0.74 |
| **number of live births** | 0.73 ± 0.09 (0-2) | 0.58 ± 0.1 (0-2) | 0.28 |
| **Gestational age in delivery (Day)** | 203.03 ± 13.29 (182-226) | 202.40 ± 12.11 (182-224) | 0.79 |
| **Mean gestational age of premature rapture of membranes (Day)** | 203.05 ± 13.22 (182-226) | 203.32 ± 15.48 (182-227) | 0.92 |

* data was shown as mean ± standard deviation (range)

**Table 3. Outcome of pregnancy in the intervention and control group**

| Groups / Outcome | | Intervention | Control | *P* |
|---|---|---|---|---|
| **amniotic fluid index (centimeters)** | | 5.25±1.65 | 4.81±1.97 | 0.18 |
| **PPROM to initial contractions (days)** | **26‴-28‴ week** | 9.5 | 5.5 | 0.08 |
| | **28‴-30‴ week** | 8.5 | 5 | 0.001 |
| | **30‴-32‴ week** | 6 | 6.5 | 0.55 |
| **Vaginal delivery** | | 34 (56.7) | 25 (41.7) | 0.1 |
| **wound infection** | | 1 (1.7) | 4 (1.6) | 0.36 |
| **APGAR score** | **First minute** | 8.02±1.26 | 7.78±1.26 | 0.31 |
| | **Fifth minute** | 9.43±0.72 | 9.40±0.94 | 0.83 |
| **neonate blood PH** | | 7.33±0.16 | 7.33±0.13 | 0.94 |
| **average birth weight** | | 1609.92±41 7.28 gr | 1452.03±342.35 gr | 0/03 |
| **neonatal sepsis** | | 0 (0) | 1(1.75) | 0.5 |
| **respiratory distress syndrome (RDS)** | | 53 (88.3) | 48 (80) | 0.21 |
| **Admission to NICU** | | 10.53±1.10 | 14.23±1.89 | 0.09 |

*Data was shown as mean ± standard deviation and Frequency (percentage)

## Discussion

In the present study, the effect of progesterone on delaying delivery after PPROM was evaluated. This intervention significantly delayed this period from a mean of 5 days to 8 in the intervention group being in the $28^{th}$- $30^{th}$ week of gestation. Also, a significant increase in the birth weight of the neonates was observed.

Norman *et al*., conducted a multi-center randomized clinical trial to investigate the effect of progesterone on the prophylaxis of preterm delivery in PPROM and found that there was no significant increase in the time period between PPROM and delivery in the intervention group. They also concluded that progesterone did not increase morbidity or mortality in the mother or the child (29). The results of this study were not in compliance to the present study, thought the difference could be because of the fact that lower doses of progesterone were used by them (200 compared to 400 mg). Another possible explanation would be the beneficence of progesterone administration in special ethnic groups or in mothers with specific risk factors, a fact that is also cited in the aforementioned study.

Meis *et al*., selected 459 patients with a previous history of preterm delivery and injected intramuscular progesterone 250 mg/weekly in one group and placebo in the other group. Preterm delivery was significantly lower in patients receiving progesterone. Neonatal complications such as intraventricular hemorrhage and necrotizing enterocolitis were also lower in this group. There wasn't any side effect reported for progesterone (30). The results followed the present study, although neonatal complications such as sepsis, respiratory distress syndrome weren't significantly reduced in the present

study.

Defonseca *et al*., conducted a study with 142 cases of PPROM which compared the use of progesterone (100 mg suppository/day) with placebo. The rate of preterm delivery was significantly reduced when they used progesterone (31). The results were in concordance to the present study using a smaller dose and the same route of administration. Further studies could be needed to determine a safe minimal and efficient dose for this route of administration.

Mirzaei *et al*., also conducted a study to evaluate the effect of progesterone on the prolongation of pregnancy in patients with PPROM. 171 patients with PPROM were selected, in group 1 (57 patients), they used 17OHP 250 mg/weekly, in group 2 (57 patients), they used 400 mg progesterone suppository/day, and in group 3 (102 patients), they didn't use any medication.The average of latent phase from rupture of membranes to delivery was 15/5 days in the first group, 15/2 days in progesterone receivers, and 11/5 days in patients with no medications. The difference was statistically significant (32). The results of the present study also proved the same fact. However, prolongation of latent phase was lower in our study. None of the patients of the present study reached 34 weeks; this could be because of the lower gestational age among our patients meaning they encountered PPROM in lower gestational age.

Maher *et al*., conducted a randomized clinical trial to compare the effectiveness of intra-muscular with vaginal suppositories and found that even in lower doses, the vaginal method was significantly superior, thus making it more beneficial for clinical use. Also, the adverse effects were almost twice as high in the intramuscular group compared to the vaginal group (14.1 % vs. 7.5%) (33).

Briery *et al*., performed another randomized controlled clinical study in which patients were injected with 250 mg of progesterone in the intervention group and placebo in the control group. They found that this procedure was not beneficial for neither the mother or the neonate in terms of morbidity and mode of delivery (vaginal vs. cesarean section) (24). The results of the present study contradicted these results. The difference could be because of the different way of delivery and higher dosage in the previous study.

Aside from the controversy of progesterone administration in PPROM patients, there remains the adherence to the evidence based guidelines. Crane *et al*., found that only half of the patients who were possible candidates for progesterone therapy ever received the treatment, and the main reason for this low status was that clinicians did not offer the option in the first place rather

than not recognizing its prophylactic effect (34).

The limitation of the present study was that it did not include enough patients to be able to generalize the results to wide scopes of patients, as there may be differences between patients in different geographical areas, which the present study is not able to determine. Also in the present study, the positive effect of progesterone was only seen between the 28$^{th}$ and thirty first week of pregnancy, and no beneficence was shown in any other time period. This could be the subject of future studies, further examining the effect of progesterone, and conducting the procedure of the present study, in larger number of patients, from multiple centers in multiple areas. Understanding of methods of diagnosing and preventing PROM and PPROM are developing at an astonishing rate, so it seems comprehensive studies, comparing these methods, would be of great merit.

Results of the present study showed that progesterone suppositories reduced the latent phase of pregnancy and increased the mean age of birth significantly, without any significant change in other complications. Thus progesterone can be prescribed for women with PPROM specially between the 28$^{th}$-30$^{th}$ week of gestation.

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**(JURNAL 2)**

PLOS ONE

RESEARCH ARTICLE

# Vaginal progesterone to prevent preterm delivery among HIV-infected pregnant women in Zambia: A feasibility study

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## Abstract

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Antenatal vaginal progesterone (VP) reduces the risk of preterm birth (PTB) in women with shortened cervical length, and we hypothesize that it may also prevent PTB in women with HIV as their primary risk factor. We conducted a pilot feasibility study in Lusaka, Zambia to investigate uptake, adherence, and retention in preparation for a future efficacy trial. This was a double-masked, placebo-controlled, randomized trial of 200mg daily self-administered VP suppository or placebo. Pregnant women with HIV who were initiating or continuing antiretroviral therapy were eligible for participation. Potential participants underwent ultrasound to assess eligibility; we excluded those ≥24 gestational weeks, with non-viable, multiple gestation, or extrauterine pregnancies, with short cervix (<2.0cm), or with prior spontaneous PTB. Participants initiated study product between 20–24 weeks of gestation and continued to 37 weeks (or delivery, if sooner). The primary outcome was adherence (proportion achieving ≥80% study product use), assessed by dye stain assay of returned single-use vaginal applicators. Secondary outcomes with predefined feasibility targets were: uptake (≥50% eligible participants enrolled) and retention (≥90% ascertainment of delivery outcomes). We also evaluated preliminary efficacy by comparing the risk of spontaneous PTB <37 weeks between groups. From July 2017 to June 2018, 208 HIV-infected pregnant women were eligible for screening and 140 (uptake = 67%) were randomly allocated to VP (n = 70) or placebo (n = 70). Mean adherence was 94% (SD±9.4); 91% (n = 125/137) achieved overall adherence ≥80%. Delivery outcomes were ascertained from 134 (96%) participants. Spontaneous PTB occurred in 10 participants (15%) receiving placebo and 8 (12%) receiving progesterone (RR 0.82; 95%CI:0.34–1.97). Spontaneous PTB < 34 weeks occurred in 6 (9%) receiving placebo and 4 (6%) receiving progesterone (RR 0.67; 95%CI:0.20–2.67). In contrast to findings from vaginal microbicide studies in HIV-uninfected, non-pregnant women, our trial participants were highly adherent to daily self-administered vaginal progesterone. The study's *a*

(P30A150410). The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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*priori* criteria for uptake, adherence, and retention were met, indicating that a phase III efficacy trial would be feasible.

## Introduction

Preterm birth (PTB) is the most common cause of neonatal death worldwide.[1] The majority of this disease burden is borne by poor countries in South Asia and sub-Saharan Africa, where access to life-saving neonatal care is often limited.[2] Many of these same countries are also affected by high rates of maternal HIV, which is associated with a 50% increased PTB risk, an effect that antiretroviral drug therapy does not appear to militate against.[3]

Antenatal progesterone—an anti-inflammatory hormone administered intramuscularly or vaginally—reduces the risk of PTB in women with prior spontaneous PTB[4] or shortened cer- vix,[5–7] and is used widely for these indications. HIV infection leads to immune activation and inflammation, both systemically and in the lower genital tract.[8, 9] While antenatal progesterone has been studied in women with a range of other PTB risk factors,[10] its efficacy in pregnancies complicated by HIV alone is unknown. We conducted a pilot randomized, dou- ble-masked, placebo-controlled trial of VP to prevent PTB among HIV-infected pregnant women in Zambia. Our overall goal was to gather feasibility data that might inform the design and implementation of a phase III efficacy trial.

## Methods

### Study design

This was a double-masked, placebo-controlled, randomized trial of VP among HIV-infected pregnant women in Lusaka, Zambia. The study was designed and conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT 2010) Statement[11] and registered with clinicaltrials.gov (NCT02970552). Its primary design has been reported else- where.[12]

### Participants

Pregnant women meeting the following criteria were eligible for enrollment: (1) 18 years of age or older; (2) viable intrauterine pregnancy confirmed by ultrasound; (3) screening ultra- sound demonstrating gestational age <24 weeks; (4) antibody-confirmed HIV-1 infection;
(5) initiating or continuing antiretroviral therapy (ART) in pregnancy; (6) ability and willing- ness to provide written informed consent; and (7) willingness to adhere to study visit schedule. We excluded women with any of the following: (1) multiple gestation; (2) non-research indica- tion for

antenatal progesterone (i.e., prior spontaneous PTB or cervical length ≤20 mm on screening ultrasound); (3) planned or *in situ* cervical cerclage; (4) evidence of threatened abor- tion, preterm labor, or ruptured membranes at the time of enrollment; (5) planned delivery prior to 37 weeks; (6) major fetal anomaly detected on screening ultrasound; (7) known uter- ine anomaly; and (8) known or suspected allergy or contraindication to VP or placebo components.

All women provided written informed consent prior to study participation. The study pro- tocol was approved by the University of North Carolina Institutional Review Board, the Uni- versity of Zambia Biomedical Research Ethics Committee, the Zambian Medicines Regulatory Authority, and the Zambian National Health Research Authority prior to study initiation.

## Procedures

Potential participants were recruited from the antenatal clinics of two public-sector health cen- ters in Lusaka. At the recruitment clinics, community educators conducted group health talks focusing on general antenatal care as well as study eligibility criteria. Interested antenatal attendees were then escorted to the study clinic for further eligibility determination. To pre- screen for eligibility, we reviewed each patient's medical record and performed an ultrasound as part of standard antenatal care. Informed consent was administered in the participants' preferred language, English, Bemba, or Nyanja. After consent, we administered a baseline questionnaire, reviewed medical records, and performed a physical exam. We also did confir- matory HIV testing (Alere Determine HIV-1/2, Abbott Diagnostics), and rapid testing for syphilis (SD Bioline Syphilis 3.0, Abbott Diagnostics), hemoglobin, and urinalysis on all participants. Participants counseled on the importance of ART and study nurses facilitated referrals for those not yet receiving treatment. Women screening positive for syphilis, anemia, or abnormal urinalysis were referred for immediate treatment at the on-site antenatal clinic.

During the screening visit, which typically coincided with first presentation to antenatal care, each participant was assigned an estimated date of delivery (EDD) by ultrasound biome- try.[13, 14] Study sonographers trained and certified by the Cervical Length Education and Review (CLEAR) program (https://clear.perinatology.org) measured transvaginal cervical length on each participant once between 16 and 24 gestational weeks.

Randomization occurred between 20 $^{0}/_{7}$ and 23 $^{6}/_{7}$ gestational weeks, inclusive. Participants were randomly assigned with equal probability into one of two study groups using a paper-based system of opaque sealed envelopes in a scheme based on random permuted blocks. Micronized progesterone (200mg) and placebo vaginal suppositories were produced by an experienced com- pounding pharmacy in Chapel Hill, NC and packaged into kits of 20 suppositories prior to being shipped to Zambia. Participants were assigned unique randomization numbers that corre- sponded to one of either four active or four placebo lot numbers. At randomization and at each follow-up visit, an on-site pharmacist masked to treatment allocation dispensed study product kits from the corresponding blinded lot. All other research staff members with direct participant contact were masked to both treatment allocation and to assigned product lot numbers.

Participants were instructed to begin daily self-administration of study product starting the day of randomization and continue until 36 $^{6}/_{7}$ weeks, membrane rupture, or delivery, which- ever occurred first. Study nurses counseled participants on correct study product use at the randomization visit and at each subsequent study visit. Participants received an instructional sheet on correct product use and storage as well as a discreet carrier, applicators for daily use, and plastic bags to facilitate the return of used applicators.

Participants were also instructed to complete a dose diary indicating when they administered study product as instructed.

After randomization, participants returned to the study clinic biweekly to replenish their study product supply and for adherence monitoring by dose diary review and collection of used applicators. Laboratory technicians masked to treatment allocation and to the contents of participant dose diaries tested all returned applicators for evidence of vaginal insertion using a validated dye stain assay (DSA).[15, 16] Each single-use vaginal applicator was treated with an inert dilute food dye (0.05% FD&C Blue No.1) that produces a distinctive streaked color pat- tern when sprayed on polyethylene plastic applicators after vaginal insertion. A senior study nurse trained in DSA performed 100% quality control of all DSA results.

## Outcomes

The primary outcome of this study was the proportion of women with adequate adherence, which we defined as using at least 80% of prescribed study product.[6, 17] Secondary outcomes

were: study uptake, retention, and preliminary efficacy. We defined study feasibility *a priori* as the following: (1) at least 50% of eligible participants agree to be enrolled; (2) at least 70% of participants achieve adequate adherence; and (3) at least 90% ascertainment of delivery out- comes (i.e., date of delivery and infant vital status).

### Statistical analysis

We calculated overall adherence as the total number of DSA-positive applicators a participant returned to the clinic divided by the number of days between the date of her randomization and her last antepartum study visit or delivery, whichever was sooner. Per-visit adherence was calculated as DSA-positive applicators returned over the number of days since the previous attended study visit. We defined uptake as the proportion of women (a) meeting initial ultra- sound eligibility criteria and (b) successfully screened who were ultimately randomized into the trial. We calculated retention at each study visit as the number of women completing scheduled visits divided by the number of participants still pregnant at the time of those visits. To quantify retention at delivery, we calculated the proportion of women randomized in the trial for whom we were able to ascertain the date of delivery and infant vital status at birth. We evaluated the association of participant demographic and clinical features on adherence and retention in univariate and multivariable regression models.

We pooled participants from both randomization groups for the overall adherence estimate and analyzed adherence between groups to investigate difference by treatment. The proportion adherent was compared between groups with the Wilcoxon rank sum test. To investigate the utility of a pre-randomization placebo run-in period, we used logistic regression to estimate whether adherence at the first visit following randomization (i.e., 2 weeks later) was predictive of adherence $>95\%$ over the remaining study period. We described the performance of dose diary estimates of adherence compared to DSA estimates by calculating sensitivity, specificity, positive predictive value, and negative predictive value with corresponding 95% exact binomial confidence intervals (CI).

In addition to our feasibility analysis, we performed secondary analyses of efficacy and safety outcomes including: (a) delivery prior to 37 weeks gestation; (b) delivery prior to 34 weeks gestation; (c) birth weight $<2500$g; (d) stillbirth; and (e) related adverse events. We undertook unadjusted analyses to calculate the risk ratio of spontaneous preterm birth $<37$ gestational weeks and spontaneous preterm birth $<34$ gestational weeks by randomization group via Poisson regression with robust error variance.

## Results

Between July 2017 and June 2018, 140 HIV-infected pregnant women were recruited and ran- domized at the Kamwala District Health Center in Lusaka (Fig 1). Of 282 women who under- went screening ultrasound, 208 (74%) met ultrasound eligibility criteria. Of these, 154 (74%) successfully completed screening procedures and 140 (67%) were randomized. Because initial accrual was slow (i.e., 18 participants randomized over 3 months), we expanded recruitment in November 2017 to the nearby Chawama First-Level Hospital and achieved a monthly accrual average of 16 participants per month for the remainder of the study.

Baseline characteristics were similar between participants randomized to progesterone (n = 70) and placebo (n = 70; Table 1). Among the 137 participants (98%) who returned for at least one follow-up study visit, mean adherence to study product was 94.3% (SD±9.4) and exceeded 90% at each study visit (Fig 2). In total, 91% (n = 125/137) of participants achieved overall adherence >80% (Table 2). Adherence was not different in women randomized to pro- gesterone (94.5±9.0%) compared to those randomized to placebo (94.2±9.9%; p = 0.99).

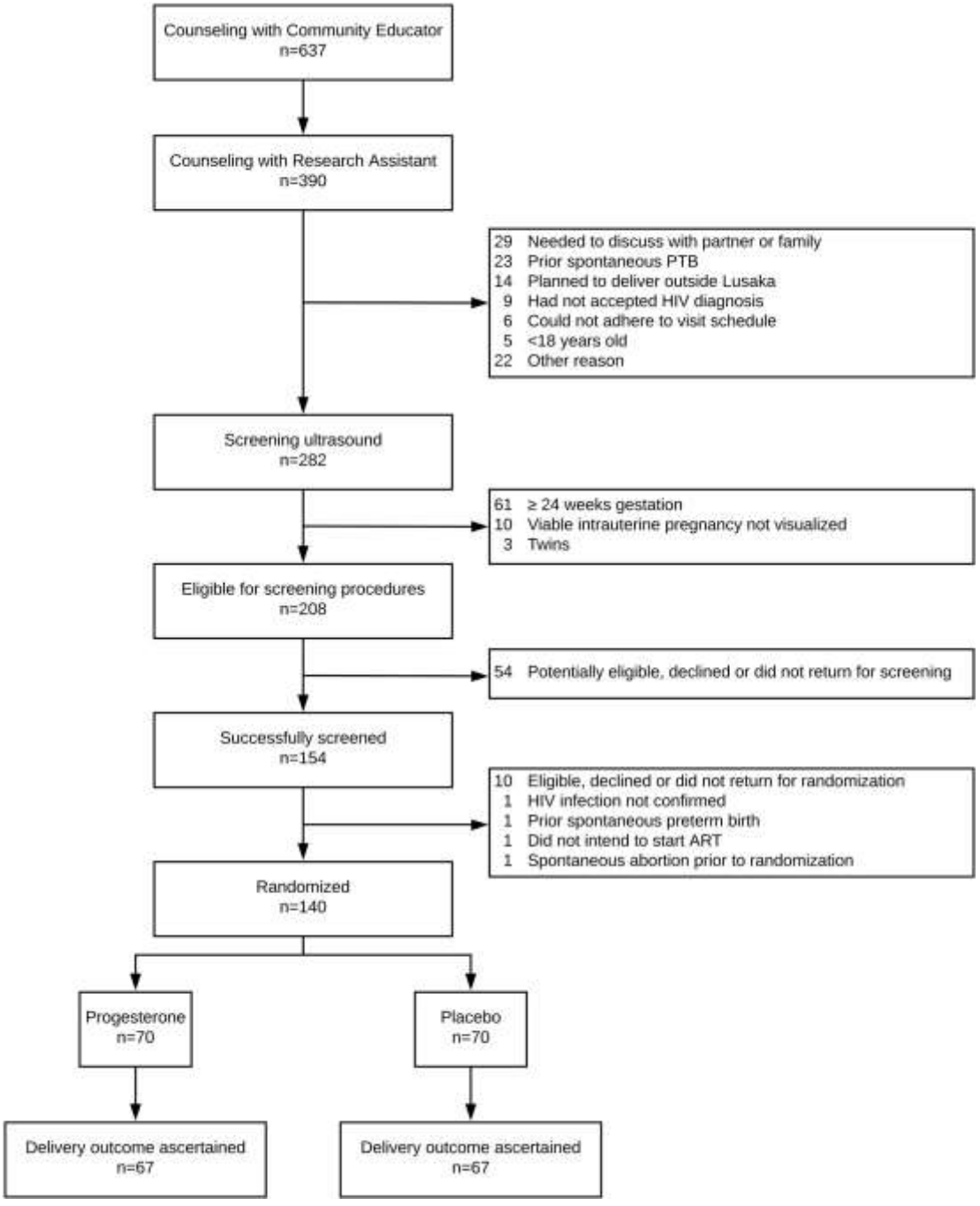


**Fig 1. Participant flowchart.**

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Increased adherence at the first study visit following randomization predicted adherence >95% at subsequent visits (OR 1.05; 95% CI 1.02–1.08). Finally, when compared to the gold standard of DSA, self-reported adherence by dose diary demonstrated sensitivity of 99.9% (99.9– 100.0%), specificity of 57.1%

(95% CI 52.1–61.9%) positive predictive value of 98.5% (98.3– 98.7%), and negative predictive value 97.5% (94.6–99.1%) when compared to DSA (Table 3).

**Table 1. Baseline characteristics of randomized participants, N = 140.**

| Characteristic | All | | Placebo | | Progesterone | |
|---|---|---|---|---|---|---|
| | Median (IQR) or N (%) | | Median (IQR) or N (%) | | Median (IQR) or N (%) | |
| Age, years | 28 | 25,33 | 28 | 25,34 | 28 | 24,34 |
| 18–24 | 34 | 24.3 | 12 | 17.1 | 22 | 31.4 |
| 25–34 | 82 | 58.6 | 45 | 64.3 | 37 | 52.9 |
| ≥35 | 24 | 17.1 | 13 | 18.6 | 11 | 15.7 |
| Education, years | 8 | 7,9 | 8.5 | 6,9 | 8 | 7,9 |
| Did not complete primary | 60 | 42.9 | 31 | 44.3 | 29 | 41.4 |
| Completed primary | 54 | 38.6 | 23 | 32.9 | 31 | 44.3 |
| Completed secondary | 26 | 18.6 | 16 | 22.9 | 10 | 14.3 |
| Marital status | | | | | | |
| Neither married nor cohabiting with partner | 19 | 13.6 | 9 | 12.9 | 10 | 14.3 |
| Either married and/or cohabiting with partner | 121 | 86.4 | 61 | 87.1 | 60 | 85.7 |
| Running water in house | 58 | 41.4 | 40 | 42.9 | 28 | 40.0 |
| Electricity in house | 124 | 88.6 | 65 | 92.9 | 59 | 84.3 |
| Roof material | | | | | | |
| Thatch | 1 | 0.7 | 1 | 1.4 | 0 | 0 |
| Tin | 73 | 52.1 | 36 | 51.4 | 37 | 52.9 |
| Slate or tile | 66 | 47.1 | 33 | 47.1 | 33 | 47.1 |
| Cooking fuel | | | | | | |
| Electricity | 27 | 19.3 | 17 | 24.3 | 10 | 14.3 |
| Charcoal / Coal | 113 | 80.7 | 53 | 75.7 | 60 | 85.7 |
| Toilet facility | | | | | | |
| Flush/pour | 48 | 34.3 | 26 | 371 | 22 | 31.4 |
| Pit/latrine | 92 | 65.7 | 44 | 62.9 | 48 | 68.6 |
| Household assets | 8 | 5,10 | 8 | 5,9 | 8 | 6,10 |
| 0–4 | 22 | 15.7 | 9 | 12.9 | 13 | 18.6 |
| 5–9 | 83 | 29.3 | 47 | 67.1 | 36 | 51.4 |
| ≥10 | 35 | 25.0 | 14 | 20.0 | 21 | 30.0 |
| BMI, kg/m2 | 26.2 | 24.3,30.1 | 26.7 | 24.3,30.1 | 25.7 | 24.1,29.7 |
| <18.5 | 1 | 0.7 | 1 | 1.4 | 0 | 0 |
| 18.5–30 | 103 | 73.6 | 50 | 71.4 | 53 | 75.7 |
| >30 | 36 | 25.7 | 19 | 27.1 | 17 | 24.3 |
| Parity | 2 | 1,3 | 2 | 1,3 | 2 | 1,3 |
| Nulliparous | 15 | 10.7 | 6 | 8.6 | 9 | 12.9 |
| Parous | 125 | 89.3 | 64 | 91.4 | 61 | 87.1 |
| Hemoglobin, mg/dL | 11.6 | 10.7,12.5 | 11.6 | 10.7,12.5 | 11.6 | 10.6,12.5 |
| <11 | 44 | 31.4 | 23 | 32.9 | 21 | 30.0 |
| ≥11 | 96 | 68.6 | 47 | 67.1 | 49 | 70.0 |
| Timing of HIV diagnosis | | | | | | |
| Prior to pregnancy | 97 | 69.3 | 52 | 74.3 | 45 | 64.3 |
| During pregnancy | 43 | 30.7 | 18 | 25.7 | 25 | 35.7 |
| Timing of ART initiation | | | | | | |
| Prior to pregnancy | 95 | 67.9 | 50 | 71.4 | 45 | 64.3 |
| During pregnancy | 45 | 32.1 | 20 | 28.6 | 25 | 35.7 |
| Syphilis screen positive | 24 | 17.1 | 13 | 18.6 | 11 | 15.7 |
| Urinary tract infection | 6 | 4.3 | 2 | 2.9 | 4 | 5.7 |
| Alcohol in pregnancy | 17 | 12.1 | 9 | 12.9 | 8 | 11.4 |

(*Continued* )

**Table 1.** (Continued)

| Characteristic | All | | Placebo | | Progesterone | |
|---|---|---|---|---|---|---|
| | Median (IQR) or N (%) | | Median (IQR) or N (%) | | Median (IQR) or N (%) | |
| Tobacco in pregnancy | 3 | 2.0 | 2 | 2.9 | 1 | 1.4 |
| EGA at screening ultrasound, weeks | 19.9 | 17.3,21.9 | 19.3 | 17.0,21.9 | 20.3 | 17.4,22.0 |
| <14 | 10 | 7.1 | 3 | 4.3 | 7 | 10.0 |
| EGA at randomization, weeks | 20.8 | 20.0,22.6 | 20.6 | 19.9,22.4 | 20.9 | 20.1,22.7 |
| Transvaginal cervical length, cm | 3.78 | 3.29,4.19 | 3.85 | 3.34,4.21 | 3.72 | 3.19,4.18 |

IQR, interquartile range; ART, antiretroviral therapy; EGA, estimated gestational age

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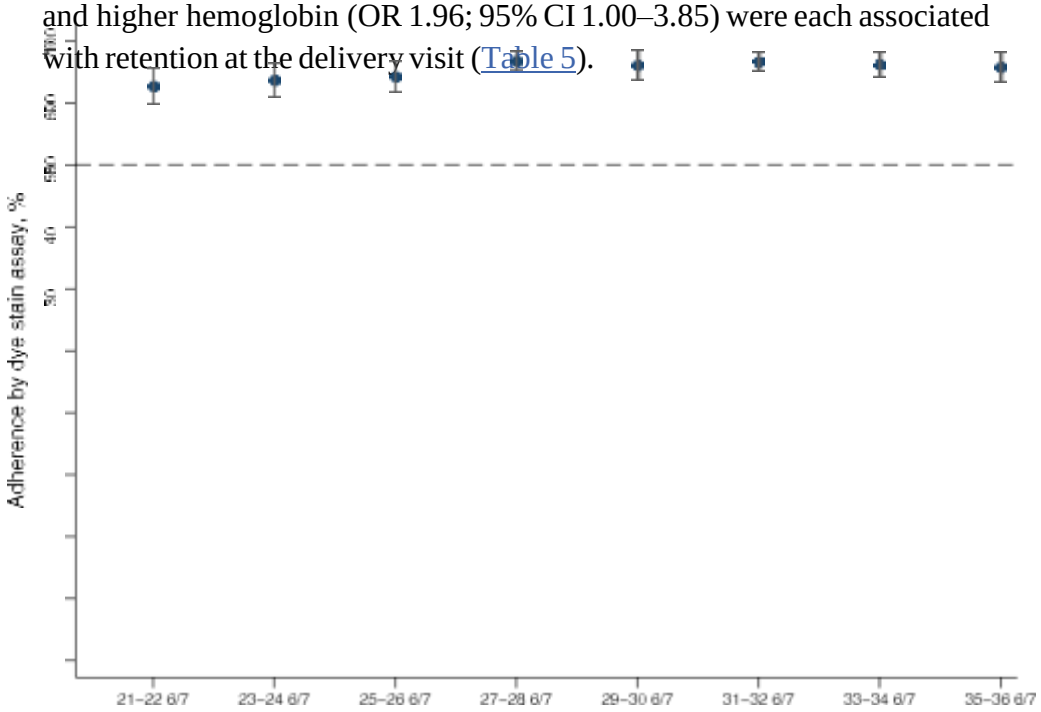
Baseline covariates associated with higher adherence determined by DSA in multivariable analysis included: having running water at home (coefficient 3.44; 95% CI 0.36–6.54) and parity (coefficient 1.40; 95% CI 0.32–2.48) (Table 4). Receipt of a new HIV diagnosis during the current pregnancy was marginally associated with lower adherence (coefficient -3.28; 95% CI -6.64–0.08).

Retention was over 90% at each scheduled follow-up study visit (Fig 2). Of the 140 random- ized, 119 (85.0%) participants attended all scheduled visits, 14 (10.0%) participants missed 1 scheduled visit, and the remaining 7 (5.0%) missed 2 or more visits. We were able to ascertain delivery outcomes (i.e., at minimum date of delivery and vital status of neonate at delivery) from 134 (96%) participants; 3 women from each randomization group (n = 6) were lost to fol- low-up. Higher baseline maternal BMI (OR 1.49; 95% CI 1.06–2.08) and higher hemoglobin (OR 1.96; 95% CI 1.00–3.85) were each associated with retention at the delivery visit (Table 5).



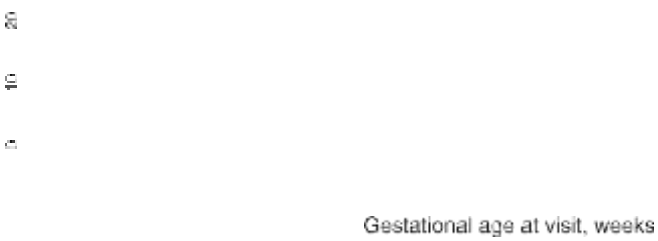



**Fig 2. Mean percent adherence by gestational age at visit, n = 137.**

https://doi.org/10.1371/journal.pone.0224874.g002

**Table 2. Adherence based on dye stain assay of returned applicators by gestational age at study visit and by visits since randomization.**

| | *n* | Overall Mean ± SD | Placebo Mean ± SD | Progesterone Mean ± SD | *p*[a] |
|---|---|---|---|---|---|
| **Overall adherence** | 137 | 94.3 (± 9.4) | 94.2 (± 9.9) | 94.5 (±9.0) | 0.986 |
| ***By gestational age at study visit*** | | | | | |
| 21.0–22.6 | 77 | 92.8 (±12.5) | 92.1 (±11.8) | 93.4 (±13.2) | 0.305 |
| 23.0–24.6 | 112 | 93.7 (±14.4) | 93.1 (±17.0) | 94.4 (±11.1) | 0.790 |
| 25.0–26.6 | 131 | 94.3 (±14.5) | 93.8 (±17.8) | 94.7 (±10.4) | 0.617 |
| 27.0–28.6 | 126 | 96.9 (±8.4) | 95.9 (±10.0) | 97.9 (±6.2) | 0.253 |
| 29.0–30.6 | 129 | 96.1 (±13.6) | 96.1 (±14.1) | 96.1 (±13.3) | 0.339 |
| 31.0–32.6 | 123 | 96.7 (±8.4) | 95.6 (±10.6) | 97.9 (±5.2) | 0.210 |
| 33.0–34.6 | 124 | 96.2 (±11.3) | 97.9 (±5.0) | 94.6 (±14.9) | 0.228 |
| 35.0–36.6 | 115 | 95.7 (±12.9) | 96.0 (±8.3) | 95.5 (±16.4) | 0.295 |
| ***By follow-up visit since randomization*** | | | | | |
| 1 | 137 | 91.3 (±16.6) | 90.5 (±18.9) | 92.1 (±13.9) | 0.148 |
| 2 | 133 | 94.9 (±11.6) | 93.9 (±13.3) | 95.9 (±9.5) | 0.108 |
| 3 | 133 | 95.6 (±13.6) | 96.1 (±13.3) | 95.0 (±14.1) | 0.261 |
| 4 | 132 | 96.4 (±11.1) | 95.7 (±13.7) | 97.2 (±7.6) | 0.520 |
| 5 | 129 | 96.4 (±11.2) | 96.2 (±10.0) | 96.5 (±12.3) | 0.554 |
| 6 | 124 | 96.8 (±9.5) | 97.0 (±7.3) | 96.7 (±11.3) | 0.222 |
| 7 | 92 | 97.3 (±5.7) | 97.3 (±5.8) | 97.2 (±5.5) | 0.543 |
| 8 | 58 | 96.3 (±13.6) | 97.5 (±4.4) | 95.4 (±17.7) | 0.676 |

SD, standard deviation

[a] ***p*** values calculated by Wilcoxon rank-sum

https://doi.org/10.1371/journal.pone.0224874.t002

Related maternal adverse events, maternal and fetal/neonatal outcomes, and efficacy out- comes were comparable between participants randomized to progesterone and those random- ized to placebo (Table 6). Of 134 randomized participants with available delivery data, 19 (14%) delivered before 37 completed gestational weeks, and 11 (8.2%) of those delivered before 34 completed gestational weeks. One preterm delivery prior to 34 weeks was provider-initiated for severe preeclampsia in a participant receiving progesterone; all other preterm deliveries were initiated spontaneously. 10 of 67 (15%) women who received placebo and 8 of 67 (12%) of those who received progesterone delivered spontaneously before 37 weeks of gestation (RR 0.80; 95% CI 0.33–1.91). Spontaneous delivery prior to 34 weeks of gestational age occurred in 6 of 67 (9.0%) women receiving placebo compared to 4 of 67 (6.0%) receiving progesterone (RR 0.67; 95% CI 0.20–2.27). Stillbirth occurred in 4 of 134 (3.0%) pregnancies, 2 receiving placebo and 2 receiving progesterone.

**Table 3. Performance of dose diary adherence assessment compared to dye stain assay.**

| | N or % (95% CI) |
|---|---|
| True positive *(DD+ DSA+)* | 11,840 |

| | |
|---|---|
| False positive *(DD+ DSA-)* | 176 |
| True negative *(DD- DSA-)* | 234 |
| False negative *(DD- DSA+)* | 6 |
| Sensitivity *Pr(DD+\|DSA+)* | 99.9% (99.9–100.0%) |
| Specificity *Pr(DD-\|DSA-)* | 57.1% (52.1–61.9%) |
| Positive predictive value *Pr(DSA+\|DD+)* | 98.5% (98.3–98.7%) |
| Negative predictive value *Pr(DSA-\|DD-)* | 97.5% (94.6–99.1%) |

CI, confidence interval; DD, dose diary; DSA, dye stain assay; Pr, probability

https://doi.org/10.1371/journal.pone.0224874.t003

**Table 4. Baseline correlates of adherence determined by dye stain assay of returned applicators.**

| | Univariate | | | Multivariable [a] | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **coeff** | **95% CI** | ***p*** | **coeff** | **95% CI** | ***p*** |
| Age, years | 0.30 | (0.00–0.60) | 0.053 | | - | |
| Education, years | 0.10 | (-0.45–0.64) | 0.727 | | | |
| Running water in house | 3.35 | (0.15–6.56) | 0.040 | 3.44 | (0.36–6.54) | 0.029 |
| Electricity in house | 3.83 | (-1.11–8.77) | 0.127 | | - | |
| Household assets | 0.50 | (-0.06–1.07) | 0.079 | | | |
| Parity | 1.56 | (0.48–2.63) | 0.005 | 1.40 | (0.32–2.48) | 0.011 |
| BMI, kg/m2 | 0.25 | (-0.05–0.55) | 0.097 | | - | |
| Hemoglobin, mg/dL | 0.33 | (-0.88–1.55) | 0.587 | | | |
| HIV diagnosed during pregnancy | -4.31 | (-7.71 to -0.93) | 0.013 | -3.28 | (-6.64–0.08) | 0.056 |
| ART initiated during pregnancy[b] | -4.17 | (-7.52 to -0.82) | 0.015 | | - | |
| Syphilis | 0.47 | (-3.73–4.68) | 0.824 | | | |
| Alcohol in pregnancy | 1.59 | (-3.25–6.43) | 0.518 | | | |
| Tobacco in pregnancy | 2.36 | (-8.56–13.3) | 0.670 | | | |
| EGA at screening | -0.04 | (-0.11–0.02) | 0.178 | | | |

CI, confidence interval; BMI, body mass index; ART, antiretroviral therapy; EGA, estimated gestational age. Coefficients (coeff) and *p* values of continuous outcome of overall adherence by baseline characteristics calculated by linear regression

[a] Multivariable analysis adjusted for listed variables.

[b] Timing of ART initiation not included in multivariable analysis given collinearity with timing of HIV diagnosis.

https://doi.org/10.1371/journal.pone.0224874.t004

**Table 5. Baseline correlates of participant retention at clinic visits and at the delivery visit.**

| **Characteristic** | **Retention at clinic visits[a]** | | | **Retention at Delivery Visit[b]** | | |
|---|---|---|---|---|---|---|
| | **coeff** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Age, years | 0.26 | (-0.35–0.86) | 0.400 | 1.04 | (0.89–1.22) | 0.602 |
| Education, years | -0.51 | (-1.60–0.57) | 0.353 | 0.81 | (0.57–1.13) | 0.208 |
| Married or cohabiting | -5.97 | (-15.25–3.30) | 0.205 | - | - | - |
| Running water in house | -1.64 | (-8.12–4.84) | 0.617 | 0.70 | (0.14–3.58) | 0.665 |
| Electricity in house | 2.25 | (-7.79–12.28) | 0.658 | - | - | - |
| Household assets | 0.50 | (-0.62–1.63) | 0.379 | 0.93 | (0.70–1.25) | 0.639 |
| Parity | 0.29 | (-1.92–2.50) | 0.797 | 1.09 | (0.60–1.96) | 0.776 |
| BMI, kg/m2 | 0.32 | (-0.27–0.92) | 0.283 | 1.49 | (1.06–2.08) | 0.020 |
| Hemoglobin, mg/dL | 2.20 | (-0.18–4.57) | 0.070 | 1.96 | (1.00–3.85) | 0.051 |
| HIV diagnosed during pregnancy | -1.31 | (-8.23–5.61) | 0.709 | 2.28 | (0.26–20.1) | 0.458 |
| ART initiated during pregnancy | 1.34 | (-25.58–28.27) | 0.922 | - | - | - |
| Syphilis in pregnancy via RPR | 1.07 | (-7.41–9.54) | 0.804 | - | - | - |
| Alcohol in pregnancy | 3.84 | (-5.93–13.60) | 0.439 | - | - | - |
| Tobacco in pregnancy | 5.95 | (-16.09–27.99) | 0.594 | - | - | - |
| EGA at screening | -0.07 | (-0.20–0.06) | 0.264 | 0.97 | (0.92–1.02) | 0.178 |

OR, odds ratio; CI, confidence interval; BMI, body mass index; ART, antiretroviral therapy; EGA, estimated gestational age

[a] coefficients and *p* values of proportion retention at clinic visits as continuous outcome calculated via linear regression

[b] odds ratios and *p* values of retention at delivery visit as dichotomous outcome calculated via logistic regression

https://doi.org/10.1371/journal.pone.0224874.t005

**Table 6. Frequency of safety and efficacy outcomes by study group.**

| Outcome | All, $N$ = 140 | Placebo, $n$ = 70 | Progesterone, $n$ = 70 | $P$[b] |
|---|---|---|---|---|
| | n (%) or median (IQR) | n (%) or median (IQR) | n (%) or median (IQR) | |
| *Related maternal adverse events*[a] | | | | |
| Headache | 25 (17.9) | 10 (14.3) | 15 (21.4) | 0.270 |
| Nausea / vomiting | 12 (8.6) | 6 (8.6) | 6 (8.6) | 1.000 |
| Lower abdominal pain | 13 (9.3) | 5 (7.1) | 8 (11.4) | 0.382 |
| Backache | 1 (0.7) | 1 (1.43) | 0 | 0.316 |
| Diarrhea | 4 (2.9) | 1 (1.43) | 3 (4.3) | 0.310 |
| Fatigue / weakness | 0 | 0 | 0 | - |
| Vaginal itching or burning | 13 (9.3) | 8 (11.43) | 5 (7.1) | 0.573 |
| Vaginal discharge | 3 (2.14) | 1 (1.43) | 2 (2.86) | 0.559 |
| Urinary tract infection | 3 (2.14) | 1 (1.43) | 2 (2.86) | 0.559 |
| *Maternal outcomes* | | | | |
| Oligo-/polyhydramnios at 32w | 0 | 0 | 0 | - |
| Gestational hypertension | 0 | 0 | 0 | - |
| Pre-eclampsia | 1 (0.7) | 0 | 1 (1.5) | 0.315 |
| Eclampsia | 0 | 0 | 0 | - |
| Antepartum hemorrhage | 0 | 0 | 0 | - |
| Preterm prelabor rupture of membranes | 0 | 0 | 0 | - |
| Cesarean delivery | 6 (4.5) | 4 (6.0) | 2 (3.0) | 0.403 |
| Median time to hospital discharge, days | 1 (0,1) | 1 (0,1) | 1 (0,1) | 0.413 |
| *Fetal / neonatal outcomes* | | | | |
| Small for gestational age (n = 128) | 35 (27.3) | 16 (25.0) | 19 (29.7) | 0.552 |
| Birthweight <2500g (n = 128) | 21 (16.4) | 12 (18.8) | 9 (14.1) | 0.474 |
| Male sex (n = 134) | 79 (59.0) | 39 (58.2) | 40 (59.7) | 0.861 |
| Median Apgar score at 1 min (n = 129) | 9 (9,9) | 9 (9,9) | 9 (9,9) | 0.456 |
| Median Apgar score at 5 min (n = 129) | 9 (9,9) | 9 (9,9) | 9 (9,9) | 0.705 |
| NICU admission (n = 134) | 10 (7.5) | 7 (10.5) | 3 (4.5) | 0.189 |
| Early neonatal death (n = 134) | 5 (3.9) | 3 (4.7) | 2 (3.1) | 0.636 |
| *Efficacy outcomes* (n = 134) | | | | |
| Preterm birth <37 weeks | 19 (14.2) | 10 (14.9) | 9 (13.4) | 0.804 |
| Spontaneous preterm birth <37 weeks | 18 (13.4) | 10 (14.9) | 8 (11.9) | 0.612 |
| Preterm birth <34 weeks | 11 (8.2) | 6 (9.0) | 5 (7.5) | 0.753 |
| Spontaneous preterm birth <34 weeks | 10 (7.5) | 6 (9.0) | 4 (6.0) | 0.511 |
| Stillbirth | 4 (3.0) | 2 (3.0) | 2 (3.0) | 1.000 |

IQR, inter-quartile range; NICU, neonatal intensive care unit

[a] Signs, symptoms, or diagnoses that started after randomization and were deemed possibly related to study product use

[b] $p$ values calculated by chi square or Wilcoxon rank sum for categorical and continuous comparisons, respectively

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## Discussion

We present the results of a pilot study evaluating the feasibility of a trial of antenatal vaginal progesterone for the prevention of preterm birth among HIV-infected pregnant women with- out other major risk factors. The study surpassed its *a priori* goals for trial uptake, study prod- uct adherence, and

participant retention, indicating that a phase III efficacy trial would be feasible in Zambia. Incidence of adverse events was similar between study groups and, while this study did not have statistical power to investigate efficacy, preliminary efficacy estimates will be used to inform sample size calculations for a full-scale trial.

Participants in both the progesterone and placebo groups had similarly high adherence to study product. The proportion of participants achieving adequate adherence—91%—was com- parable to or higher than reported in three other major trials of vaginal progesterone, includ- ing one conducted in the UK (94%),[17] and two others that enrolled across multiple international sites (89% and 69%, respectively).[6, 18] In these prior studies, adherence was assessed through participant interviews, dose diaries, and/or counting of unused medication at follow-up visits. One strength of our trial was its use of DSA, a method validated to objectively assess adherence.[15, 19] We also studied participant report as a secondary measure and found dose diary to be a reliable measure of product use when participants were adherent (high sensitivity), but a poor measure in the relatively rare instances of non-adherence (low specificity). However, DSA testing of 100% of returned applicators could be prohibitively resource-inten- sive in a full-scale trial, which is likely why previous studies of vaginal progesterone have relied on other methods to monitor adherence. We hypothesize that women may have been moti- vated to insert study product by the knowledge that returned applicators would be tested, so a larger trial might benefit from requesting participants to return all used applicators and then only testing a random subset from each participant to confirm adherence.

A key factor in our decision to undertake a pilot study in Zambia was concern that women may not consistently use a daily vaginal product. Some vaginal microbicide studies in HIV- uninfected, non-pregnant women in sub-Saharan Africa reported substantial discrepancies between self-reported adherence and objective measures such as DSA and plasma drug concentration monitoring.[15, 20] While many factors that may have contributed to low adher- ence in microbicide trials did not directly apply to our pregnant population already infected with HIV, we did observe some similar associations between study product adherence and par- ticipant characteristics such as older age and higher parity.[20, 21] Qualitative interviews in vaginal microbicide trials revealed a number of explanations for low adherence, including a lack of confidence in the efficacy of investigational products, unwanted side effects of vaginal discharge and interference with sexual behavior, and perceived stigmatization associated with using antiretroviral medication despite being HIV-negative.[20, 22] However, altruistic motivations among pregnant women towards their fetuses may have contributed to the high adher- ence observed in our study, outweighing negative perceptions of research participation or bothersome side effects. Similar findings have been reported to explain higher ART adherence and attendance at clinic visits during pregnancy.[23] Alongside this pilot study, we conducted individual semi-structured interviews with participants to explore the acceptability of partici- pation in the trial, results from which are forthcoming. Another study reported high accept- ability of antenatal progesterone—both vaginal and

intramuscular formulations—among pregnant women in Zambia,[24] and we anticipate similar findings.

More than half of potentially eligible participants were successfully randomized into this trial, surpassing our target set for uptake. The study team faced initial difficulties in identifying a sufficient number of potentially eligible participants solely from the district clinic where the study was conducted, in response to which we expanded recruitment to a second nearby pub- lic-sector facility. This expansion substantially accelerated recruitment and accrual. Despite an accrual velocity that lagged below initial targets, our study demonstrated a similar overall uptake proportion in comparison to other published VP trials.[6, 17, 18]

High participant retention in this study was likely aided by a number of supportive reten- tion efforts. At each study visit, participants were provided transportation reimbursement plus a snack or a meal at longer visits. The value of these reimbursements was approved by the local ethics authority. Study staff placed telephone calls to any participant who missed an appoint- ment, and community staff made home visits to participants unreachable by telephone. We also performed weekly telephone follow-up for participants still pregnant at 40 or more weeks

of gestation. Research nurses ascertained key delivery details (i.e., date of delivery and infant vital status) initially over the phone for those who reported having delivered, and encouraged delivered participants to return to the study clinic as soon as possible to review delivery records and ascertain full details of the delivery and subsequent course. The value of social and struc- tural support for improving retention and adherence is well understood,[25] and we hypothe- size that biweekly follow-up visits in conjunction with the described supportive measures played an important role in participant retention.

We acknowledge several limitations of the current study. First, participants were recruited from a small catchment area in a single urban setting within Zambia. This geographical focus, as well as other baseline characteristics of our participants, might limit the extent to which trial feasibility could be generalized to studies in other geographical areas, or to younger and pri- miparous women. Second, while we reported a high positive predictive value of the dose diary (i.e., women with high self-reported adherence by dose diary were likely to return DSA-posi- tive applicators), we note that the specificity of dose diary reporting was much lower (i.e., in instances when the DSA was negative, the dose diary was marked as adherent nearly half of the time). Given the relatively few cases of non-adherence, our study might have missed latent pat- terns of non-adherence that would occur in a trial with lower overall adherence. However, we suspect that high desirability of successful childbearing in Zambia, request for return of all used applicators, and intensive retention measures will encourage high adherence and reten- tion in a larger trial. Finally, the DSA method itself is not perfect. DSA performance can be affected by the specific dyes and applicator plastics used, and it has been most widely studied in the context of microbicides.[15, 16, 19, 26] Whether the medication being inserted affects the validity of DSA is unknown. DSA positivity does not provide definitive information on whether the suppository (and not just the applicator) was actually inserted. These limitations notwithstanding, our pilot study used a plastic material, dye, and evaluation method that have shown optimal sensitivity and specificity in multiple validation studies.[16, 19]

## Conclusion

This pilot is the first published randomized trial of vaginal progesterone to prevent HIV- related preterm birth. If shown to be effective in a full-scale trial, antenatal progesterone could reduce the high societal and healthcare costs of care for premature infants and of medical and social support for long- term sequelae. Based on high uptake, adherence, and retention in this pilot study, we conclude that a full-scale efficacy trial of vaginal progesterone to prevent pre- term birth in HIV-infected gravidas would be feasible in our setting.

## Supporting information

**S1 Fig. CONSORT Checklist.**
(PDF)

**S2 Fig. Study Protocol.**
(PDF)

## Author Contributions

**Conceptualization:** Joan T. Price, Bethany L. Freeman, Bellington Vwalika, Helen B. Mulenga, Jeffrey S. A. Stringer.

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**Supervision:** Joan T. Price, Winifreda M. Phiri, Bethany L. Freeman, Bellington Vwalika, Jen- nifer Winston, Chileshe M. Mabula-Bwalya, Helen B. Mulenga, Jeffrey S. A. Stringer.

**Validation:** Jennifer Winston.

**Writing - original draft:** Joan T. Price, Chileshe M. Mabula-Bwalya, Jeffrey S. A. Stringer.

**Writing - review & editing:** Joan T. Price, Winifreda M. Phiri, Bethany L. Freeman, Belling- ton Vwalika, Jennifer Winston, Chileshe M. Mabula-Bwalya, Helen B. Mulenga, Jeffrey S. A. Stringer.

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**LAMPIRAN 2**

**LEMBAR KONSUL KIAN**

## LEMBAR KONSULTASI

KELOMPOK : 19

DOSEN PEMBIMBING : Ns. Isra Nur Utari Syachnara Potaboga, M.Kep

| No. | Hari/Tanggal | Materi Bimbingan | TTD Dosen | Keterangan |
|---|---|---|---|---|
| 1 | 22/04/2021 | Sistematika penyusunan KIAN |  | Penjabaran sitem penyusunan KIAN |
| 2 | 23/04/2021 | Mengajukan tema |  | Revisi |
| 3 | 6/05/2021 | Mengajukan jurnal terkait tema |  | Revisi |
| 4 | 21/05/2021 | Mengajukan tema |  | Acc |
| 5 | 24/05/2021 | Jurnal penelitian |  | Acc<br>Silahkan lakukan 27nalisa jurnal dan buat ECBR |

| | | | | |
|---|---|---|---|---|
| 6 | 18/06/2021 | ECBR |  | Revisi Tambahkan scenario klinis, critical appraisal dan sesuaikan contoh ECBR |
| 7 | 02/07/2021 | Mengajukan refisi ECBR |  | Revisi sesuai ECBR |
| 8 | 21/07/2021 | ECBR |  | Acc |
| 9 | 26/07/2021 | Persiapan seminar KIAN |  | Ditambahkan jurnal pembanding lebih baik |
| 10 | 29/07/2021 | Mengajukan ECBR dengan jurnal pembanding |  | Acc |
| 11 | 04/08/2021 | Mengajukan laporan KIAN |  | Acc |
| 12 | 22/08/2021 | Mengjukan jadwal seminar KIAN |  | Acc |

| | | | | |
|---|---|---|---|---|
| 13 | 26/08/2021 | Mengajukan hasil revisi seminar |  | Pisahkan antara laporan KIAN dan EBCR |
| 14 | 2/09/2021 | Mengajukan laporan EBCR |  | Ditambahkan nama pembimbing pada logo, halaman pengesahan, persetujuan dan referensi |