PRETERM BIRTH

Abstracts 9-17

9 Low dose aspirin for the prevention of recurrent preterm labor (APRIL): a randomized controlled trial

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OBJECTIVE: To evaluate the effectiveness of aspirin compared to placebo for the prevention of preterm birth (PTB) when initiated in early pregnancy in women with a previous spontaneous preterm birth (SPTB).

STUDY DESIGN: We performed a multicenter, double-blind, randomized controlled trial (APRIL, NTR 5675). We recruited women with a singleton pregnancy and a history of SPTB (singleton pregnancy 22+0 - 37+0 weeks) following either preterm prelabor rupture of membranes or spontaneous contractions. After informed consent, participants were randomly assigned to daily aspirin (80 mg) or placebo started between 8+0 and 16+0 weeks gestation. Treatment was continued until 36+0 weeks gestation or delivery. Primary outcome was PTB before 37+0 weeks gestation. Secondary outcomes included a composite of poor neonatal outcome (bronchopulmonary dysplasia, periventricular leukomalacia >grade 1, intraventricular hemorrhage >grade 2, necrotizing enterocolitis >stage 1, retinopathy of prematurity, culture proven sepsis or perinatal death). A sample of 384 women was required to detect a PTB reduction from 36 to 23% (α-error 0.05, β-error 0.2). Analyses were performed by intention to treat.

RESULTS: Between May 2016 and June 2019, we randomly allocated 194 women to aspirin and 193 to placebo. The PTB rate was 21.2% in the aspirin group versus 25.4% in the placebo group (RR 0.83; 95% CI 0.58-1.2). SPTB occurred in 20.1% versus 23.8% of women (RR 0.84; 95% CI 0.58-1.2). For women who were ≥80% compliant with study medication, PTB rates were 18.5% versus 24.8% (RR 0.75; 95% CI 0.46-1.2). The poor neonatal outcome rate was 4.6% versus 2.6% (RR 1.79; 95% CI 0.61 to 5.3). There were no significant differences in maternal morbidities such as hypertensive disorders and postpartum hemorrhage.

CONCLUSION: Our data did not demonstrate a reduction of PTB in women with a previous SPTB who used aspirin 80 mg. The RR for PTB is comparable to larger studies on aspirin in other groups of women. A small reduction of PTB from aspirin in women with a previous SPTB cannot be excluded with the current sample size.

Outcome	Aspirin (n=194)	Placebo (n=193)	RR (95% CI)
Preterm birth <37+0	41 (21.2%)	49 (25.4%)	0.83 (0.58-1.20)
Spontaneous	39 (20.1%)	46 (23.8%)	0.84 (0.58-1.23)
Indicated	2 (1.0%)	3 (1.6%)	0.66 (0.11-3.93)
Preterm birth <34+0	18 (9.3%)	17 (8.8%)	1.05 (0.56-1.98)
Preterm birth <28+0	7 (3.6%)	5 (2.6%)	1.39 (0.45-4.31)
Composite poor neonatal outcome	9 (4.6%)	5 (2.6%)	1.79 (0.61-5.25)
Women with ≥80% medication compliance			
Preterm birth <37+0	23/124 (18.5%)	30/121 (24.8%)	0.75 (0.46-1.21)

10 A randomized trial of 17-hydroxyprogesterone caproate to prevent preterm birth among women living with HIV

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OBJECTIVE: Women with HIV face an increased risk of preterm birth (PTB), the leading worldwide cause of child death. 17 alpha-hydroxyprogesterone caproate (17P) has been shown in some trials to reduce early delivery among women with a prior spontaneous PTB.

STUDY DESIGN: We conducted a randomized, double-masked, placebo-controlled trial of 17P among HIV-infected women attending public-sector antenatal care in Lusaka, Zambia. We excluded women with prior spontaneous PTB or multiple gestation. Participants were randomly allocated to receive weekly intramuscular injections of 250mg 17P or placebo, starting between 16 and 24 gestational weeks and continuing until 36 6/7 weeks, delivery, or stillbirth, whichever occurred first. The trial's primary outcome was delivery < 37 weeks or stillbirth at any gestational age. We compared the risk of pre-

specified outcomes between randomization groups using an intent-to-treat approach.

RESULTS: 800 women were randomized between Feb 2018 and Jan 2020. Baseline characteristics were similar between treatment groups. Adherence to study drug was high in both groups (98%) and delivery outcomes were ascertained for all 800 participants. The primary outcome occurred in 36 (9.02%) participants assigned to 17P and 36 (8.98%) assigned to placebo (risk difference = 0.05; 95% CI: -3.92, 4.01). In a pre-specified analysis excluding provider-initiated PTB phenotypes, 25 (6.36%) women randomized to 17P delivered spontaneously before 37 weeks compared to 26 (6.63%) of those receiving placebo (risk difference = -0.27; 95% CI: -3.72, 3.18). The timing of antiretroviral therapy initiation relative to conception did not affect the risk of the primary outcome nor did it modify the effect of the intervention. Related adverse events were low and occurred at similar rates between the study groups.

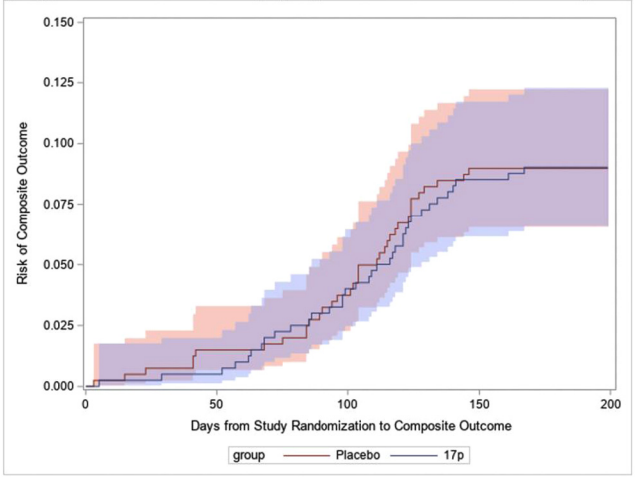
CONCLUSION: In this trial with complete ascertainment of outcomes and very high adherence to study drug, weekly antenatal 17P injections did not reduce the composite risk of preterm delivery or stillbirth among women with HIV in Zambia.

Table 1. Outcomes by treatment assignment in the IPOP trial, February 2018 – August 2020, Lusaka, Zambia

	17P n = 399		Placebo n = 401		Risk Difference (%) (95% CI)	Risk Ratio (95% CI)
	n	%	n	%		
Primary composite outcome						
Delivery < 37 weeks and/or stillbirth[a]	36	9.02	36	8.98	0.05 (-3.92, 4.01)	1.01 (0.65, 1.56)
Livebirth < 37 weeks	26	6.52	25	6.23	0.28 (-3.10, 3.67)	1.05 (0.61, 1.78)
Stillbirth at any gestational age	10	2.51	11	2.74	-0.24 (-2.45, 1.98)	0.91 (0.39, 2.13)
Secondary outcomes						
Delivery < 37 weeks	31	7.77	35	8.73	-0.96 (-4.77, 2.85)	0.89 (0.56, 1.41)
Spontaneous delivery < 37 weeks[b]	25	6.36	26	6.63	-0.27 (-3.72, 3.18)	0.96 (0.56, 1.63)
Provider-initiated delivery < 37 weeks[c]	6	1.60	9	2.40	-0.80 (-2.80, 1.21)	0.67 (0.24, 1.86)
Delivery < 34 weeks	14	3.51	16	3.99	-0.48 (-3.11, 2.15)	0.88 (0.44, 1.78)
Delivery < 28 weeks	3	0.75	5	1.25	-0.50 (-1.87, 0.88)	0.60 (0.15, 2.51)

Abbreviations: CI, confidence interval
[a] Chi-square test for difference in proportions $p = 0.98$
[b] Excludes 15 provider-initiated preterm births
[c] Excludes 51 spontaneous preterm births

Figure 1. Cumulative-incidence curves for risk of composite outcome (i.e., preterm birth or stillbirth) by days from randomization and study arm

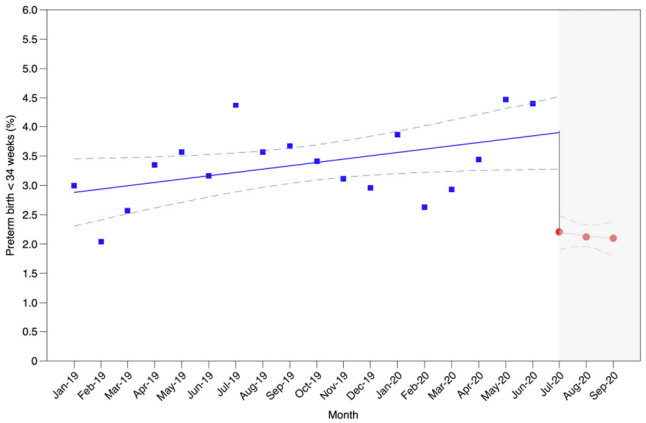


OBJECTIVE: It has been suggested that lockdown during the COVID-19 pandemic decreased prematurity rates. We investigated the impact of lockdown on obstetric outcomes.

STUDY DESIGN: We performed a cohort study on women who gave birth at three maternity hospitals in metropolitan Melbourne, Australia, between Jan 1st, 2019 and Sept 16th, 2020. Data were extracted from the common birth registry of the three maternities. The second lockdown started July 8th, 2020 and required people to stay at home, with limited exemptions. We performed interrupted time-series analysis to compare the monthly rates of preterm birth before 34 weeks prior to and after July 2020. We also compared the group of women who delivered between July and September 2020 to the group of women who delivered during the same period in 2019.

RESULTS: A total 15,394 women gave birth. Interrupted time-series analysis demonstrated a significantly lower monthly rate of deliveries before 34 weeks of gestational age after July 2020 (Figure 1; p = 0.001). There were 2,207 deliveries between July to Sept. 2019 and 1,870 deliveries between July to Sept. 2020. Baseline characteristics were comparable, except for a significantly difference in twins (1.5% in 2020 versus 2.6% in 2019, p = 0.012). After excluding women with pregnancies complicated by major fetal abnormalities or stillbirth, the risk of preterm delivery before 34 weeks was much lower in patients who delivered between July and September 2020 (2.1% versus 3.3%, RR 0.64, 95% CI 0.44 to 0.94, p = 0.022) (Table 1). Similar patterns were observed for iatrogenic and spontaneous preterm birth at different gestational ages. The effect persisted after logistic regression adjustment for multiple pregnancies (adjusted OR 0.65, 95% CI 0.46 to 0.96, p = 0.028). The decrease in prematurity was not at the cost of an increase in stillbirth or undetected small for gestational age neonates.

CONCLUSION: Strict lockdown has a strong impact on iatrogenic and spontaneous prematurity rates. While returning to normal, which aspects of lockdown contributed to this unprecedented effect should be evaluated.



11 Impact of the coronavirus pandemic lockdown on obstetric outcomes

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