30 Vaginal versus Intramuscular Progesterone for Prevention of Recurrent Preterm Birth (VIP): a randomized controlled trial

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OBJECTIVE: To determine whether vaginal progesterone is superior to intramuscular 17-hydroxyprogesterone caproate (17OHPC) in prevention of recurrent preterm birth (PTB) in singletons with prior spontaneous preterm birth (sPTB).

STUDY DESIGN: This is a multi-center randomized controlled trial of patients eligible for progesterone therapy with a singleton gestation and prior sPTB. A sample size of 95 participants in each arm was calculated to detect a 50% difference in PTB risk (80% power and 2-sided α=0.05) based on a 36% recurrent PTB rate with 17OHPC. Participants randomized 1:1 to 200mg vaginal progesterone daily or 250mg 17OHPC injection weekly from 16-36 weeks. The primary outcome was PTB < 37 weeks. Secondary outcomes included PTB < 34 and < 28 weeks, mean gestational age at delivery, neonatal morbidity/mortality, and measures of adherence. This was a pragmatic trial, there was no exclusion based on adherence and progesterone was ordered through insurance. Analysis was by intention to treat. Chi square and student t-test were used to compare outcomes, as appropriate. Kaplan-Meier survival curve used to compare latency to delivery. P < 0.05 considered significant. Registered on clinicaltrials.

RESULTS: Of 205 randomized, 94 in vaginal progesterone and 94 in 17OHPC groups were included (Figure A). Those assigned to vaginal progesterone initiated therapy earlier (16.9 ± 1.4 vs 17.8 ± 2.5 wks, p=0.001), but overall continuation of assigned formulation until delivery was similar (73% vs 69%, p=0.61). There was no significant difference in PTB < 37 wks (31% vs 38%, p=0.28). Those assigned vaginal progesterone had a later mean gestational age at delivery (37.4 ± 2.7 vs 36.3 ± 4.1 wks, p=0.047) with a trend of increased latency (log rank p=0.055) (Figure B). Other outcomes were similar (Table).

CONCLUSION: Vaginal progesterone is not superior to 17OHPC in prevention of recurrent preterm birth, but may increase latency to delivery. Both vaginal progesterone and 17OHPC may be considered for use in prevention of recurrent PTB, taking into consideration patient preferences and ability to obtain medication in a timely fashion.

31 Effect of the ALPS trial on steroid and assisted ventilation use in late preterm infants

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OBJECTIVE: To examine the effects of the ALPS (Antenatal Late Preterm Steroids) Trial on late preterm steroid use and any potential effects on neonatal outcomes.

STUDY DESIGN: Interrupted time series analysis of singleton, liveborn, non-anomalous infants born at 34-36 weeks of gestation to people without pre-existing diabetes using US birth certificate data. The period from 2/16 (ALPS trial publication on nejm.org) to 10/16 (publication of updated ACOG Committee Opinion) was considered the “dissemination” (or washout) period. We examined the immediate effect of the ALPS trial dissemination on antenatal steroid use and 1) any assisted ventilation and 2) ventilation use for >6 hours. Monthly rates before and after the dissemination period were compared between 1/2014 and 12/2019, controlling for seasonal variation in the outcomes and the monthly distribution of deliveries by week of gestation. An interaction term for race/ethnicity was added to the same model to examine variation among different populations.

RESULTS: Figure 1 shows the unadjusted monthly rates of steroid and assisted ventilation use along with adjusted trend lines before and after the dissemination period. There was a 7.32-percentage point (pp) increase in steroid use (95%CI 6.82, 7.81) after the dissemination of the ALPS trial, corresponding to a more than 2.5-fold immediate increase in its use. There was a 0.53-pp reduction in any assisted ventilation use (95%CI -0.82, -0.25); no significant difference in ventilation use > 6 hours was observed. Steroid administration and effects on ventilation use varied by race/ethnicity, with White, non-Hispanic women experiencing the highest increase in steroid use and observed neonatal benefits (Table 1).

CONCLUSION: Within the limitations of the birth certificate data, these findings suggest the number needed to treat in the overall population with late preterm steroids is approximately 14 to prevent any adverse perinatal outcomes. We hypothesized that wild fire exposure triggers a fetal inflammatory response and aimed to quantify fetal Hofbauer cells in placental biopsies.

STUDY DESIGN: We collected placentas from uncomplicated pregnancies exposed to wildfire smoke during the 2018 California fire season undergoing elective terminations during the first and second trimester from November 2018 to February 2019. Full thickness placental biopsies were formalin-fixed and paraffin-embedded. Daily values of the Air Quality Index (AQI, from US EPA) for each sample and average daily AQI levels during the gestation were calculated. Immunostaining against CK7 and CD68 was performed to identify intravillous fetal Hofbauer cells. Ten representative sections per biopsy were examined in a blinded fashion. The total number of CD68+ cells were normalized against the total villous cross-sectional area to obtain a weighted CD68 score. We assessed the relationship of CD68 score with the cumulative or average AQI via linear regression.

RESULTS: Twelve biopsies were examined with gestational ages ranging from 7-24 weeks. The average daily AQI among the samples was 46.11. Nine of the twelve samples were gravid during a wildfire event, with average time from peak AQI to specimen collection of 8 weeks (58 days) (Fig A). The range of CD68 scores was 155.6 to 602.3, with an average score of 426. Our results revealed a significant positive correlation between CD68 score in placental chorionic villi and cumulative (r=0.6, p= 0.03) or average daily AQI (r=0.6, p= 0.03). We saw that with every 10-fold increase in average AQI, CD68 score increased by a factor of 100.68 (Fig B).

CONCLUSION: Our results suggest that wildfire smoke exposures are associated with increased presence of fetal Hofbauer cells in mid-gestation placenta, a phenomenon linked with inflammation and impaired placental function.