Thursday, February 4, 2016 • 1:15 PM – 4:00 PM • Hilton Atlanta - Salon West

PREMATURITY

Abstracts 9-19

Moderators: Uma Reddy, MD; Joe Simpson, MD, Senior Vice President for Research and Global Programs, March of Dimes

9 Risk of preterm birth by transvaginal ultrasound cervical length in low risk singleton pregnancy

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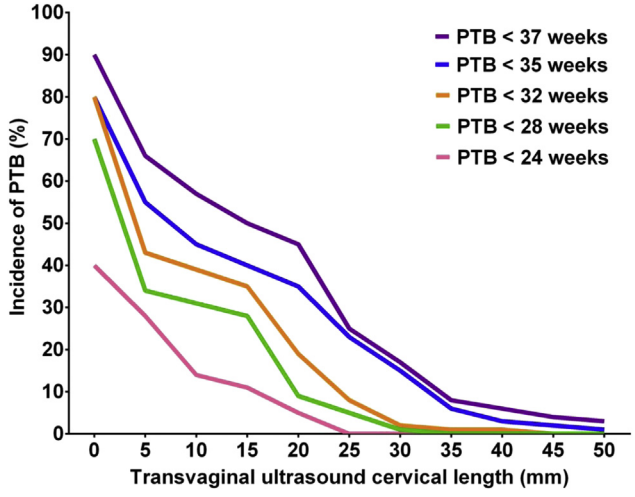
OBJECTIVE: To evaluate the risk of preterm birth (PTB) at different gestational age cut offs in women without prior PTB based on transvaginal ultrasound cervical length (TVUCL) measurement.

STUDY DESIGN: Retrospective observational study of women with singleton pregnancy without prior PTB, with TVUCL measurements between 16 to 23 6/7 weeks at Thomas Jefferson University Hospital from July 1995 to December 2013. Exclusion criteria were history of cone biopsy, management with progesterone, pessary, or cerclage and fetal anatomic or genetic anomalies. Primary outcome was the risk of PTB <37 weeks, <35 weeks, <32 weeks, <28 weeks and <24 weeks stratified by TVCL.

RESULTS: 2037 women were evaluated with TVUCL. Mean gestational age at TVUCL was 20.2±1.2 weeks, N=1053 (51.9%) were nulliparous, N=1008 (49.5%) were African American, and N=213 (10.5%) smoked during pregnancy. TVUCL ≤25mm was seen in 66 (3.3%) women. The overall incidence of PTB <37 weeks was 143 (7%). The incidence of PTB <37 weeks, <35 weeks, <32 weeks, <28 weeks and <24 weeks by TVUCL is shown in the figure.

CONCLUSION: There is a significant indirect correlation between a shorter TVUCL and higher incidence of PTB at all gestational age cut offs. The variation in the risk for early and very early PTB as well as the overall risk of PTB is important for the counseling and management of women with different degrees of short TVUCL.



10 Targeted liposomes direct the delivery of indomethacin to the uterus enhancing its tocolytic efficacy to reduce uterine contractions and preterm birth rate

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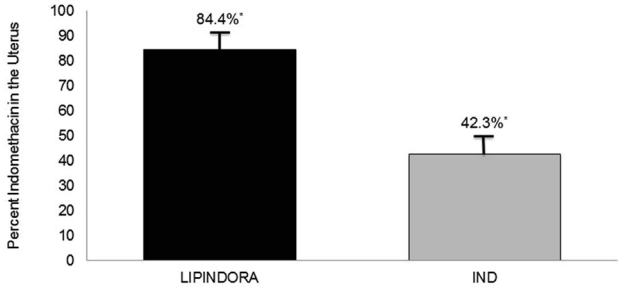
OBJECTIVE: We have previously shown that liposomes (LIP) reduce placental passage of indomethacin (IND) while preserving its prostaglandin production inhibitory effects. Our objective was to determine whether liposomal IND designed specifically to target the uterus would inhibit uterine contractions and reduce preterm birth rate.

STUDY DESIGN: Multi-lamellar LIP were fabricated with a 150-200 nm size, loaded with IND and decorated with oxytocin receptor antagonist to create a targeted liposomal indomethacin (LIPINDORA). Twelve CD1 mice on gestational day (GD) 19 received either LIPINDORA or IND via tail vein injection (IND dose of 1 mg/kg). After 4 hours, the uterine tissue was retrieved to measure IND levels. In a separate set of CD1 mice (GD 19, n=6), the uterine tissue was obtained and placed in an organ bath chamber to measure isometric tension. After incubation with LIPINDORA, IND or saline (SAL), changes in uterine contractility and prostaglandin (PGE2) levels were determined. Finally, preterm labor was induced in CD1 mice on GD 16 with 25 mcg of lipopolysacharride (LPS). LIPINDORA, IND or SAL was administered daily via tail vein injection. The preterm birth rate defined as delivery prior to GD18 was determined in each group. One way ANOVA was used to compare outcomes among groups.

RESULTS: The percentage of IND levels in the uterine tissue was doubled in animals given LIPINDORA compared to IND alone (Fig. 1). LIPINDORA significantly increased the percent inhibition of uterine contractions compared to saline, (LIPINDORA: 56.0 ± 6.4%* vs. IND: 34.3 ± 5.9% vs. SAL: -12.8 ± 18.4%*, p* =<0.003). PGE2 levels were significantly reduced in the uterus exposed to LIPINDORA and IND compared to SAL, (LIPINDORA: 4127.9 ± 1178.6 vs. IND: 2587.4 ± 676.5 vs. SAL: 40188.7 ± 15,555.6 pg/mL, p=<0.019). LIPINDORA significantly reduced the rate of LPS-induced preterm birth compared to SAL (Fig. 2). Although the preterm birth rate was less with LIPINDORA compared to IND alone, this was not statistically significant.

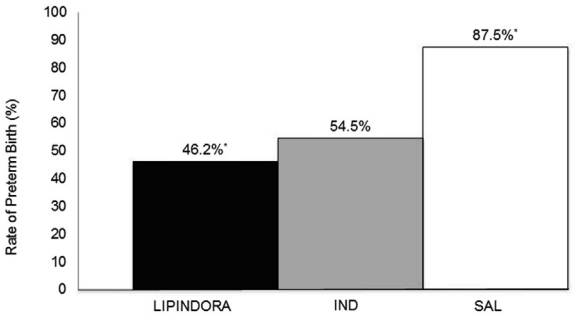
CONCLUSION: By doubling the concentration of IND in the uterus while preserving its pharmacological effects, LIPINDORA significantly reduced uterine contractions and preterm birth. This is the first targeted LIP delivering IND directly to the uterus to enhance its tocolytic efficacy.

Figure 1. Percent indomethacin in the uterus of mice who received the targeted liposomal indomethacin compared to indomethacin alone



LIPINDORA- Targeted Liposome, IND- Indomethacin
Values are reported as mean ± sem
*p-value = 0.008

Figure 2. Preterm birth rate of mice who received targeted liposomal indomethacin compared to indomethacin alone



LIPINDORA- Targeted Liposome, IND- Indomethacin, SAL- Saline
*p-value = 0.029

11 Aspirin triggered-Resolvin D1 (AT-RvD1) inhibits inflammation-induced preterm birth (IIPTB) in a mouse model

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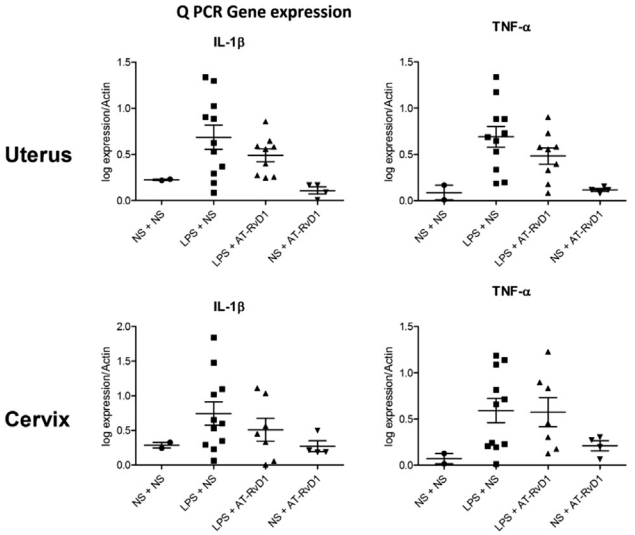
OBJECTIVE: To determine if AT-RvD1, a derivative of the omega 3 fatty acid, DHA, will reduce preterm delivery rate in a validated mouse model of IIPTB. We also tested the effect of treatment with AT-RvD1 on pro- and anti-inflammatory cytokines in maternal mouse uterus, cervix, placenta, serum, and amniotic fluid as well as fetal brain.

STUDY DESIGN: We used a mouse model of IIPTB. Dams received intrauterine injection of normal saline (NS) or lipopolysaccharide (LPS 25 mcg) per animal on E17. AT-RvD1 was injected intraperitoneally 1h after laparotomy. A total of 4 groups were utilized: LPS + NS (n=19), LPS + AT-RvD1 (n=18), NS+NS (n=3) and NS+RvD1 (n=5). Animals were evaluated for signs of preterm birth (PTB), which was defined as delivery of at least one pup within 24 hours of surgery. All animals were sacrificed at 24h and tissues collected. RT-QPCR analysis was performed for mRNA expression of IL-4, IL-6, IL-10, IL-1β, TNF-α and NOS-1. Luminex cytokine assay was performed to measure protein levels (GM-CSF, TNF-α, IL-1β, IL-4, IL-6, IL-12, IFN-γ, IL-10, IL-5, IL-2) in amniotic fluid and maternal serum.

RESULTS: The PTB rate was decreased to 28% in LPS+AT-RvD1 group in comparison with the positive control group (LPS+NS). An increase in IL-1β and TNF-α expression was seen in the uteri and cervices of LPS treated animals as compared to controls. This effect was less prominent in the fetal brain and placenta. Treatment with AT-RvD1 resulted in a decrease in mRNA expression of IL-1β and TNF-α in the uterus and cervix and a decrease in NOS1 expression in the placenta. AT-RvD1 had no effect on cytokine expression in the fetal brain. AT-RvD1 treatment also decreased IL-12 levels in maternal serum.

CONCLUSION: Treatment with AT-RvD1 decreased PTB in a mouse model of IIPTB. This decline was associated with a decrease in mRNA expression of IL-1β and TNF-α in the uterus and cervix. Further studies are needed to determine whether AT-RvD1 may have a therapeutic role in IIPTB prevention. Supported by The Pregnancy Foundation's Thomas Garite Mini-Sabbatical Grant.



12 Genetic variation may influence response to 17-alpha hydroxyprogesterone caproate (17P) for recurrent preterm birth (PTB) prevention

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OBJECTIVE: We hypothesized that maternal genotype affects variable response to 17P for recurrent PTB prevention.

STUDY DESIGN: Secondary analysis of the GPN prospective multicenter cohort study of PTB. Women (n=106) with ≥1 prior singleton SPTB who received 17P during pregnancy were classified as 17P responders (RES) or non-responders (NRES) in 2 ways: (A) a difference in delivery gestational age (GA) between 17P treated and untreated pregnancies (RES=delivered ≥3 weeks later w/17P vs. without 17P), and (B) Term vs. PTB in the studied pregnancies (RES=delivered ≥37 weeks w/17P). To assess genetic variation, all