Week 4: Neonatology

Neonatal General: Placenta and Cytokines

Friday, July 24 2:30-4:00 pm EDT

Moderators
Camille Fung
Joyce Marie Koenig

EDT	Abstract	Title	Presenting Author
2:30 pm		Introduction & General Information	
2:35 pm	3379903	Age-dependent changes in T cell populations and cytokine responses in mice.	Mariana Brewer
2:45 pm	3380618	Pro-inflammatory cytokine responses to early, repeated allogeneic packed red blood cell transfusion in extremely preterm neonates	Tara Crawford
2:55 pm	3379356	PLACENTAE SUPPORTING MALE OR FEMALE FETUSES SHOW SEXUAL DIMORPHISM IN A MOUSE MODEL OF FETAL GROWTH RESTRICTION ORIGINATING FROM HYPETENSIVE DISEASE OF PREGNANCY	Camille Fung
3:05 pm	3374469	Vitamin C Supplementation to Pregnant Smokers is Associated with Improved Placental Circulation and Gene Expression	Cindy McEvoy
3:15 pm	3377899	Temporal profile of cytokine levels in association with placental pathology in extremely preterm infants	Hussein Zein
3:25 pm	3332362	Treatment With Lansoprazole Improves Pregnancy Outcome In Mice	Christina Konecny
3:35 pm	3377525	Relating Complex Fetal and Placental Growth in High-Risk Pregnancies with Neonatal Outcomes Using Quantitative MRI	Ariunzaya Amgalan
3:45 pm		Wrap Up	

Note: Schedule subject to change based on presenter availability.

CONTROL ID: 3379903

TITLE: Age-dependent changes in T cell populations and cytokine responses in mice.

PRESENTER: Mariana Rae Brewer

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: T cell, Immune Development , Cytokines.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Infants respond to infections differently than do older children and adults. These differences in part reflect a lack of prior antigen exposure that is required for the development of a mature adaptive immune response. The result may be a lack of the memory T cell repertoire required to mount an adequate response to bacterial, fungal and viral infections.

Objective: Assess age-dependent changes in splenic T cell subsets in mice.

Design/Methods: C57/BL6 mice aged 1 day, 1 wk, 4-5 wks, 10 wks and 16 wks were sacrificed. These ages correlate to 23-24 weeks premature, full-term infant, child, adolescent and adult. Spleens, which represent the available mature immune cell population, were harvested and cells were stained for flow cytometry to assess T cell subsets. T cells from 1 wk- and 4 wk-old mice underwent in vitro T cell receptor (CD3/CD28) stimulation. IL2, IL17, IFNg, and TNFa production in CD4 and CD8 T cells was assessed. Data were analyzed using unpaired 2-tailed T test or one-way ANOVA as appropriate.

Results: The number of total splenic CD4 and CD8 T cells increased over time ($p < 0.01$). Total memory and effector memory CD4 and CD8 T cells are rare at birth and, in the absence of exposure to infection or inflammation, increased with chronologic age ($p < 0.01$). This pattern was also observed in naïve CD4 and CD8 T cells and in $FoxP3^+$ CD4 T cells (Treg cells) (Fig 1). In 4 wk-old mice, a greater proportion of CD4 T cells and a lower proportion of CD8 T cells made IFNg compared to 1 wk-old mice. There was no significant difference in the proportions of CD4 and CD8 T cells making IL2, IL17, and TNFa between 1 wk- and 4 wk-old mice (Fig 2).

Conclusion(s): These data demonstrate that neonatal mice lack T cells, which assist in mounting an early and effective immune response during infection. Even in the absence of exposure to infection, the number of T cells increases with age. The number of memory T cells also increases with age, and this expansion is associated with increased ability of CD4 T cells to make IFNg. These differences could account for observed clinical differences in the response to infection between newborns and adults and warrant further investigation of the effects on infection and the mechanisms of development of these changes over time.

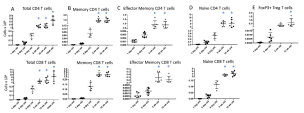

Fig. 1. T cell subsets in the spleen increased over time. * p < 0.01, one-way ANOVA with sidak's correction for multiple comparisons (A) Total CD4 and CD8 T cells (x 10^) (B) Total Memory CD4 and CD8 T cells (x 10^) (C) Total effector memory CD4 and CD8 T cells (x 10^) (D) Total Naive CD4 and CD8 T cells (x 10^) (E) Total Treg cells (x 10^).

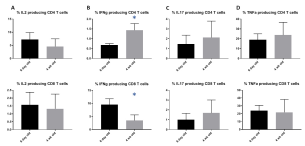

Fig. 2. In vitro cytokine production by CD4 and CD8 T cells at 1 week and 4 weeks old. * p < 0.01, unpaired 2 tailed T-test (A) Proportion of CD4/CD8 T cells producing IL2 (B) Proportion of CD4/CD8 T cells producing IFNg (C) Proportion of CD4/CD8 T cells producing IL17 (D) Proportion of CD4/CD8 T cells producing TNFa.

IMAGE CAPTION:

CONTROL ID: 3380618

TITLE: Pro-inflammatory cytokine responses to early, repeated allogeneic packed red blood cell transfusion in extremely preterm neonates

PRESENTER: Tara Crawford

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Transfusion, Immunomodulation, inflammation.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Very preterm newborns typically receive up to 3-5 packed red blood cell (PRBC) transfusions, often early, during their NICU admission. Despite increasing awareness of the association of PRBC transfusion with the incidence of major neonatal morbidities and increases in pro-inflammatory cytokines, consistent with transfusion related immunomodulation (TRIM), research has focused on single transfusions in the convalescent period weeks after preterm birth.

Objective: With pathophysiologic processes contributing to the development of significant morbidities associated with prematurity likely to start soon after delivery, we investigated the pro-inflammatory response to early, repeated transfusion exposure.

Design/Methods: The transfusion related cytokine response to the first 3 PRBC transfusions was investigated in transfusion naive infants < 30 weeks' gestation. Plasma cytokines were measured by multiplex ELISA.

Results: The median (IQR) age was 3 days (1-9) at 1st transfusion, 7 (3 – 20) at the 2nd, and 18 (7 – 28) at the 3rd. Baseline cytokine concentrations did not differ between the three transfusions. IL-17α and TNFα did not change following the first transfusion but both increased significantly following the second ($p<0.05$) and third transfusion exposures ($p<0.01$). While no post-transfusion difference in circulating IL-1 β, IL-6, and IL-8 concentrations were seen following the first and second transfusions, all increased following the third transfusion (IL-1 β, $p<0.01$; IL-6, $p<0.01$; and IL-8, $p<0.05$).

Conclusion(s): To our knowledge this is the first report of early and repeated transfusion related alterations following repeat transfusion exposure in the very preterm newborn. The current data suggests that the potential for TRIM is present in the initial days following birth rather than confined to later in the post-natal period. We postulate that this represents a potential pathophysiologic mechanism underlying the association between PRBC transfusion exposure to increased incidence of significant morbidity and mortality in the very preterm newborn.

(No Image Selected)

CONTROL ID: 3379356

TITLE: PLACENTAE SUPPORTING MALE OR FEMALE FETUSES SHOW SEXUAL DIMORPHISM IN A MOUSE MODEL OF FETAL GROWTH RESTRICTION ORIGINATING FROM HYPETENSIVE DISEASE OF PREGNANCY

PRESENTER: Camille Fung

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: fetal growth restriction, placenta, sexual dimorphism.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: In our mouse model of fetal growth restriction (FGR) originating from hypertensive disease of pregnancy (HDP), we have previously published that in early HDP (embryonic day=E 15.5 in a 20-day gestation), FGR female fetuses preserved their body weight by increasing their placental weights compared to sham females. FGR males, in contrast, weighed less despite no change in placental weights compared to sham males (Gibbins et al. 2018). We set out to investigate the potential molecular pathways responsible for such sex-dimorphic differences by examining the protein expression of genes critical for placental angiogenesis including hypoxia-inducing factors (HIFs) and their downstream target genes that involve the Wnt pathway.

Objective: To determine placental protein abundance of HIF1 and 2 alpha and HIF1 beta, plus Wnt1, 2, 4, 5a/b, and 7b ligands, Fzd7 (a Wnt receptor), WIF1, and nuclear beta catenin (a readout of the Wnt pathway) in E15.5 male and female sham and FGR placentae.

Design/Methods: FGR was induced via an established model of thromboxane A_2-analog infusion from E12.5 in pregnant C57Bl/6 mice mimicking human HDP (Fung et al. 2011). Sham surgery mice acted as controls. Caesarian sections were performed at E15.5 and placentae were harvested. Nuclear and cytoplasmic protein fractions were isolated from sham and FGR placentae. Western immunoblotting was used to assess protein abundance of aforementioned genes. Either YY1 or GAPDH were used for loading controls.

Results: None of the HIFs were altered in either FGR male or female placentae compared to their sham counterparts at E15.5. FGR female placentae however increased Wnt1 (8.82±1.86 vs. 3.58±1.10), WIF1 (8.88±0.63 vs. 6.67±0.67), and nuclear beta catenin (0.943±0.07 vs. 0.660±0.028) compared to sham female placentae. FGR male placentae decreased Wnt5a/b (0.314±0.12 vs. 0.717±0.11) but increased WIF1 (4.83±0.26 vs. 3.61±0.45) compared to sham males.

Conclusion(s): Despite no change in any of the HIFs examined, we saw opposing downstream changes involving genes of the Wnt pathway in FGR female and male placentae that are known to be critical for angiogenesis. The fact that FGR female placentae increase their Wnt protein expression likely represent a compensatory mechanism to augment placental angiogenesis in face of HDP and may explain their ability to preserve body weight at this age. The investigation of other classic angiogenesis genes such as the angiopoietins, PDGF, and PIGF is warranted.

(No Image Selected)

CONTROL ID: 3374469

TITLE: Vitamin C Supplementation to Pregnant Smokers is Associated with Improved Placental Circulation and Gene Expression

PRESENTER: Cindy T. McEvoy

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Vitamin C, Smoking in pregnancy, Placenta function.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Smoking during pregnancy is associated with increased resistance of the umbilical-placental circulation with reduced blood flow to the fetus. Over 50% of female smokers continue to smoke in pregnancy, leading to significant health risks to offspring including preterm birth, growth restriction, and cardiopulmonary complications later in life. We have shown in a non-human primate (NHP) model that vitamin C supplementation prevented nicotine induced changes in placental volume blood flows.

Objective: To determine whether vitamin C supplementation to pregnant smokers protects against consequences on umbilical-placental circulation.

Design/Methods: A sub-study done within a randomized controlled trial (RCT) which demonstrated vitamin C supplementation vs. placebo to pregnant smokers significantly increased airway function in the offspring at 3 months of age (AJRCCM 2019). At 34 weeks of gestation, standard pulsed Doppler ultrasound was used to obtain measurements of the intraabdominal umbilical artery and vein in 55 randomized smokers and 33 pregnant never smokers studied as a reference group (Table 1). Blood flow velocity waveforms were used to calculate umbilical artery pulsatility index and umbilical vein volume blood flow and velocity. The mean of 3 measurements was used in statistical analysis. An obstetrician reviewed all ultrasounds for quality. In an overlapping but separate set of patients from the same RCT we performed placental RNA-seq to identify potential mechanisms underlying changes in umbilical-placental circulation.

Results: Umbilical vein Doppler velocity was significantly increased in vitamin C vs. placebo treated smokers (Table 2). Similar to results in NHPs, there was a trend for a greater umbilical vein volume blood flow in vitamin C vs placebo treated smokers. Umbilical artery pulsatility index was increased in smokers vs. non-smokers but this difference was not significant after adjusting for the gestational age at ultrasound (p=0.059). Placental RNA-seq in 18 nonsmokers, and 28 vitamin C and 27 placebo treated smokers identified 2,214 genes differentially expressed in nonsmokers vs placebo, 488 genes in vitamin C vs. placebo smokers; identifying many genes in vascular development (Table 3).

Conclusion(s): In this sub-study, vitamin C supplementation to pregnant smokers was associated with improved umbilical-placental circulation. Vitamin C appeared to normalize gene expression toward the level of nonsmokers in pathways highly relevant to vasculature and cardiac development.

Table 1. Demographics of Infants Studied by Doppler Ultrasound in Sub-Study

	Vitamin C treated smokers (n=29)	Placebo treated smokers (n=28)	Reference group of non-smokers (n=33)	p-value for vitamin C versus placebo
Gestational age at ultrasound (weeks)	33.8 (0.3)	33.6 (0.4)	35.0 (0.3)	0.51
Birthweight (grams)	3142.4 (105.2)	3175.9 (97.1)	3071.8 (76.3)	0.81
Sex (M/F)	18/11	14/12	14/19	0.54

Values are Mean (SEM)

Table 2. Doppler Ultrasound Results

	Vitamin C treated smokers (n=29)	Placebo treated smokers (n=26)	Reference group of Nonsmokers (n=33)	P value for vitamin C versus placebo
Vmax (Umbilical vein Doppler velocity (cm/sec))	27.88 (1.29)	23.49 (1.24)	27.71 (1.50)	0.025
IAUV (Intra-abdominal umbilical vein diameter (cm))	0.614 (0.014)	0.609 (0.019)	0.621 (0.019)	0.919
CSA (Cross sectional area of the umbilical vein (cm2))	0.299 (0.015)	0.299 (0.021)	0.310 (0.019)	0.769
UAPI (Umbilical artery pulsatility index)	0.991 (0.033)	0.967 (0.033)	0.893 (0.028)	0.760
QUV (Umbilical vein volume blood flow (mL/min))	249.8 (17.7)	208.9 (19.3)	250.4 (16.4)	0.133
Fetal heart rate (beats per minute)	141.3 (2.2)	137.3 (2.1)	142.7 (1.8)	0.165

Values are Mean (SE). P values adjusted for gestational age at ultrasounds; CSA: calculated as π(IAUV diameter (cm)/2); QUV calculated as 0.5 x Vmax x CSA x 60

Table 3. Top 10 Enriched Gene Ontology Terms from ConsensusPathDB#

Gene Ontology Description	q-value#
Blood vessel morphogenesis	0.001132
Vasculature development	0.001132
Cardiovascular system development	0.001132
Circulatory system development	0.001132
MAPK cascade	0.00552
Atrial septum development	0.005331
Response to growth factor	0.012451
Regulation of membrane depolarization during action potential	0.012451
Wound healing, spreading of cells	0.013518
Cardiac atrium development	0.019732

Input to analysis included 149 nominally significant in both comparisons of placebo vs nonsmokers and placebo vs vitamin C; q-value = p-value corrected for multiple testing using the false discovery rate method

IMAGE CAPTION:

CONTROL ID: 3377899

TITLE: Temporal profile of cytokine levels in association with placental pathology in extremely preterm infants

PRESENTER: Hussein Zein

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Cytokines, inflammation, Extremely preterm infants.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Despite many advances, prematurity continues to be a major cause of neonatal mortality and morbidity, with placental abnormalities and inflammation being a common etiological factor. Inflammation-induced release of cytokines, chemokines and growth factors ("cytokines") is important to both the inflammatory process and cell signaling, which can influence brain development. However, even the association between known causes of inflammation (e.g. chorioamnionitis) and brain injury in extremely preterm infants remains controversial, and there are few studies evaluating the effect of other types of placental pathologies. Hence, there is a need to study the association of placental pathology and cytokine profiles in extremely preterm infants because of the potential implication for brain development.

Objective: To evaluate the relationship between placental pathology and the temporal profiles of cytokine levels in extremely preterm infants.

Design/Methods: This was a prospective cohort study of extremely preterm infants, < 29 weeks gestational age, admitted to the NICU between June 2017 and July 2018 (n=55). Levels of 27 cytokines were measured in blood from the umbilical cord at birth, and directly from the babies at 24-72 hours, and 21-28 days of life. Cytokine levels were assayed using the Bio-Rad Multiplex System. Placental pathology was categorized by a neuropathologist, blinded to neonatal variables, according to the 2016 Amsterdam consensus and grouped as normal (N), inflammation (I), vasculopathy (V), or combined vasculopathy and inflammation (V+I). Nonparametric Kruskal Wallis and Friedman tests were used to compare between and within the groups.

Results: Of the 55 infants enrolled, complete data from 42 was analyzed. Cord blood median levels of cytokines differed between groups for Eotaxin ($p = 0.038$), G-CSF ($p = 0.023$), IFN-γ ($p = 0.002$), IL-1ra ($p < 0.001$), IL-4 ($p = 0.005$), IL-8 ($p = 0.010$), MCP-1 ($p = 0.011$), and TNFα ($p = 0.002$), with the highest levels found in the V+I group as compared to the

N, I and V groups. Post hoc analysis revealed sex differences in group I, where levels of FGF-basic (p = 0.03), G-CSF (p = 0.048), IL1b (p = 0.038), IL-1ra (p = 0.005), IL-8 (p = 0.005), MIP-1α (p = 0.048) and TNFα (p = 0.048) were higher in females.

Conclusion(s): Specific types of placental pathology may be associated with differential neonatal cytokine profiles, and, in particular, assays from cord blood may help infer placental pathology and stratify risk for brain injury in extremely preterm infants.

Table 1. Neonatal, prenatal and obstetrical characteristics between placental pathology groups

Characteristics*	Placental pathology group				P value
	N (n = 8)	I (n = 12)	V (n = 13)	V+I (n = 9)	
GA, weeks, median (IQR)	26 (25-27)	26 (25-27)	26 (24-27)	27 (24-27)	0.469
Birth weight (g), median (IQR)	926 (721.5-1346.3)	855 (778-1136)	780 (617.5-990)	800 (585-1039.5)	0.368
Male gender	7 (88)	5 (41.7)	8 (62)	6 (67)	0.222
5 minutes Apgar, median (IQR)	7 (5-8)	8 (7-9)	7 (6-9)	6 (6-8)	0.642
SNAP II PE, median (IQR)	35.5 (20.3-41.8)	27.5 (11-32.8)	19 (10-34)	18 (8-64.5)	0.640
Outborn	1 (12.5)	0	2 (15.4)	1 (11.1)	0.596
Maternal age, median (IQR)	32 (26.5-33.8)	31 (27-33.8)	31 (24.5-36.5)	31 (23.5-36)	0.985
Gravida, median (IQR)	3 (1.3-4)	2 (1.3-3.8)	1 (1-2)	1 (1-4.5)	0.161
Smoking	2 (25)	0	0	2 (22.2)	0.088
Alcohol	3 (37.5)	0	1 (7.7)	0	0.023
Illicit drugs	1 (12.5)	0	0	2 (22.2)	0.148
Diabetes	0	2 (16.7)	1 (7.7)	1 (11.1)	0.653
Hypertension	0	0	5 (38.5)	1 (11.1)	0.013
Assisted conception	1 (12.5)	2 (16.7)	3 (23.1)	2 (22.2)	0.941
Multiple pregnancy	3 (37.5)	1 (8.3)	4 (30.8)	0	0.115
Antenatal steroids	6 (75)	12 (100)	13 (100)	9 (100)	0.03
APH	6 (75)	3 (25)	1 (7.7)	2 (22.2)	0.009
PPROM>24 hours	3 (37.5)	5 (41.7)	1 (7.7)	5 (55.6)	0.099
Clinical chorioamnionitis	0	3 (25)	0	1 (11.1)	0.134
Caesarean section	6 (75)	4 (33.3)	9 (69.2)	5 (55.6)	0.203

* Data presented as frequencies with percentages. SNAP II PE = Score for Neonatal Acute Physiology II Perinatal Extension; APH = antepartum hemorrhage; PPROM = preterm premature rupture of membranes

Table 2. Significant differences in "cytokine" levels between placental pathology groups

Variable*	Placental pathology groups				P value
	N (n = 8)	I (n = 12)	V (n = 13)	V+I (n = 9)	
T1					
Eotaxin	14.8 (9.3-18)	16.5 (13.6-33.4)	20.1 (15.4-28.2)	24.2 (21.3-33.6)	0.038
G-CSF	319.1 (239.1-650.5)	613.4 (243.2-1134.7)	241.9 (187.7-924.3)	749.7 (481.2-2311.8)	0.023
IFN-γ	7 (3.6-9)	17.7 (7.4-26.7)	9.5 (6.6-15)	42.4 (17.3-72.8)	0.002
IL-1ra	310.9 (215.6-891.3)	2672.9 (745.3-10350.8)	255.4 (143.9-1092.5)	7312.1 (2312-16131.1)	<0.001
IL-4	0.7 (0.4-0.9)	1.1 (0.7-1.6)	1 (0.8-1.5)	1.6 (1.4-3.5)	0.005
IL-8	37.6 (23-46.1)	112.2 (56.4-240.3)	42 (22.8-131.7)	197.1 (84.1-597)	0.010
MCP-1	79.3 (57.4-148.6)	64.2 (22.1-188.4)	134.4 (80.1-276.7)	238.6 (184.6-476)	0.011
TNFα	45.3 (30.2-60.9)	84.1 (42.9-156.8)	34.9 (27.7-57.8)	87.7 (63.1-138.9)	0.002
T2					
IFN-γ	45.3 (23.3-82.3)	24 (12.3-34.8)	79.1 (54-119.1)	68.3 (34.5-86)	0.008
IL-4	1.1 (1-1.5)	0.6 (0.5-1)	1.6 (0.9-2.4)	1.5 (1.1-2.5)	0.017
MCP-1	642.1 (187.5-980.5)	197.4 (87.6-297.7)	963.1 (381.5-1859)	580 (106.8-1210.6)	0.033

* Data presented as medians (IQR), pg/ml

Table 3. Sex differences in specific protein levels in the placental groups with pathology

Placental group	Variable*	Sex		P value
		Male (n=5)	Female (n=7)	
Group I		T1		
	FGF-basic	34.9 (34.4-41.9)	86.5 (40.0-109.2)	0.03
	G-CSF	227.5 (134.5-593.9)	754.7 (606.8-2198.3)	0.048
	IL-1β	0.6 (0.4-1.1)	3.8 (0.9-10.8)	0.038
	IL-1ra	572.9 (265-1824.5)	10098.0 (2959.1-13019.1)	0.005
	IL-8	56.4 (40.3-81.6)	213.1 (117.7-271.0)	0.005
	MIP-1α	6.7 (4.1-9.6)	16.3 (7.5-33)	0.048
	TNFα	47.2 (37.4-72.6)	130.1 (76-192.2)	0.048
		T2		
	TNFα	71.9 (49.4-81.3)	41.8 (36.9-51.6)	0.018
		Male (n=8)	Female (n=5)	
Group V		T1		
	FGF-basic	47.5 (37.4-55)	25.3 (22.2-39.5)	0.019
		T2		
	IFN-γ	99.8 (76.2-143.6)	54.7 (37-78.2)	0.045
		T3		
	IL-4	2.4 (1.8-3)	1.6 (1.1-1.7)	0.019
	IL-5	25.8 (23.6-34.5)	16.9 (16.2-19.8)	0.017
	VEGF	327.5 (259.2-390.9)	223 (192.7-242.6)	0.019
		Male (n=6)	Female (n=3)	
Group V+I		T1		
	IL-9	203.9 (164.8-245.6	273.9 (265.1-331.8)	0.024
		T2		
	IP-10	532 (301.9-1100.7)	169 (41-231.3)	0.048

* Data presented as medians (IQR), pg/ml

Figure 1. Temporal changes in protein levels

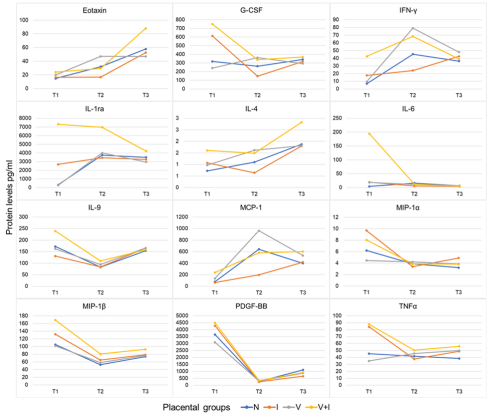

IMAGE CAPTION:

CONTROL ID: 3332362

TITLE: Treatment With Lansoprazole Improves Pregnancy Outcome In Mice

PRESENTER: Christina M Konecny

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Preterm Birth, Drug Repurposing, Inflammation.

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Using a computational drug repositioning approach that leverages data to uncover novel therapeutic uses for drugs already developed and evaluated for safety, we identified 83 that may be effective for preventing spontaneous preterm birth (sPTB). Of these, lansoprazole, a proton pump inhibitor (PPI) currently used for treating gastric ulcers, was identified with a strong profile.

Objective: Thus, we evaluated the effect of lansoprazole on pregnancy outcome using a mouse inflammation model of fetal wastage.

Design/Methods: Pregnant FVB mice were treated on E6.5–E8.5 with saline (IP), progesterone (P4, 80 mg/kg IM), mineral oil (P4 vehicle, IM), lansoprazole (PPI, 24 mg/kg IP), or 5% DMSO (PPI vehicle, IP). P4 served as a positive control as it is currently indicated for preventing sPTB. At E7.5, 2h after treatment, mice were given lipopolysaccharide (LPS, 100 µg/kg IP) to induce inflammation. Control mice received no LPS (Saline only). Mice were then sacrificed at E12.5 and the number of viable fetuses and resorbed concepti (identified by their hemorrhagic/necrotic appearances and absence of fetuses) was recorded for each pregnancy.

Results: In LPS Only-treated pregnant mice, fetal survival significantly decreased 57% compared with that for pregnant controls (Saline Only), as expected. Treatment with P4 (Oil+LPS) or PPI (DMSO+LPS) vehicle had no affect on fetal survival compared with LPS-Only-treated dams. Most importantly, treatment with P4 or PPI significantly increased fetal survival after LPS treatment (P4+LPS, 1.7-fold; and PPI+LPS, 2.7-fold) compared with LPS-Only-treated dams and were similar to that of controls.

Conclusion(s): We conclude that the administration of lansoprazole may have protective effects in an LPS-induced inflammation mouse model of fetal wastage. These promising results demonstrate the potential effectiveness of using computational drug repurposing approaches for identifying compounds, such as PPIs, that might be effective in preventing sPTB.

TABLE:

Number of Viable Fetuses (means±SD, n=number of pregnancies)

Group	Saline Only	LPS Only	Oil + LPS	DMSO + LPS	P4 + LPS	PPI + LPS
Viable Fetuses	**8.4 ± 1.0*** (7)	3.6 ± 4.0 (10)	1.3 ± 2.4 (6)	2.9 ± 4.9 (7)	**6.4 ± 3.1*** (5)	**9.6 ± 1.1*** (5)

*p<0.01 compared with LPS-Only-treated pregnant dams

IMAGE CAPTION:

CONTROL ID: 3377525

TITLE: Relating Complex Fetal and Placental Growth in High-Risk Pregnancies with Neonatal Outcomes Using Quantitative MRI

PRESENTER: Ariunzaya Amgalan

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS:

SESSION TITLE: Neonatal General: Placenta and Cytokines |Neonatal General: Placenta and Cytokines

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Placental function is influenced by both maternal and fetal health. Maternal and pregnancy-related co-morbidities, including hypertension, diabetes and autoimmune conditions are associated with adverse perinatal outcomes, yet the direct impact of maternal health on placental growth, and by extension, fetal well-being, is poorly understood.

Objective: This study aims to assess placental and fetal growth trajectories, including fetal-placental volume ratios as a measure of placental efficiency, in high-risk pregnancies using quantitative fetal magnetic resonance imaging (MRI).

Design/Methods: We performed a prospective observational study of fetal and placental development in high-risk pregnancies. Pregnant women > 18 weeks gestation with singleton pregnancies and a significant medical condition were recruited to undergo fetal MRI. T2 weighted-images of the maternal abdomen were acquired; fetal body, fetal brain, and placenta were identified through semi-automated pipelines, and manually corrected using ITK-SNAP software. Volumes were calculated in mm^3 and fetal-placental ratios were derived. Clinical data including gestational age (GA) at delivery and birthweight (BW) were obtained, and categorized as appropriate for gestational age (AGA, BW 10-90^{th} %), small for gestational age (SGA, BW ≤ 10^{th} %) or large for gestational age (LGA, BW ≥ 90^{th} %) based on published growth charts. Unpaired t-tests compared fetal-placental volumes and ratios between AGA, SGA and LGA groups.

Results: Fifty (50) high-risk women with hypertensive disorders of pregnancy, diabetes mellitus, thyroid and maternal mental health disorders underwent MRI (Tables 1-2). Infants born SGA had lower placental volumes and fetal brain volumes compared to AGA counterparts, and a higher fetal brain: placental ratio (Table 3); of note, only 1/3 of SGA infants were suspected to have fetal growth restriction in utero. Infants born LGA had greater placental volumes than both AGA and SGA infants, and a trend for lower fetal body: placental ratios (Table 3).

Conclusion(s): Quantitative fetal MRI can describe in-utero fetal-placental growth in high-risk pregnancies. Placental volumes, along with fetal-placental ratios, are associated with neonatal growth status at delivery. This may have potential to aid in early detection of placental insufficiency and potential dysfunction in high-risk pregnancies.

Table 1: Demographic data for high-risk pregnancies with appropriate-for-gestational age (AGA), small-for-gestational age (SGA) and large-for-gestational age (LGA) offspring

	AGA (n=32)	SGA (n=12)	LGA (n=6)
Maternal Age (years)	35.05 ± 5.01	34.87 ± 7.46	36.75 ± 2.97
GA at MRI (weeks)	30.99 ± 4.82	29.51 ± 5.77	31.31 ± 5.63
Male fetal sex	16 (50%)	4 (33%)	2 (33%)
GA at birth (weeks)	38.95 ± 1.77	37.23 ± 4.21	39.10 ± 0.82
BW (grams)	3206 ± 419	2201 ± 630*	4112 ± 275*
BW percentile	42.45 ± 20.32	3.13 ± 3.31*	92.87 ± 3.77*

* Significantly different from AGA at p < 0.0001

Table 2: Maternal characteristics for high-risk pregnancies with appropriate-for-gestational age (AGA), small-for-gestational age (SGA), and large-for-gestational age (LGA) offspring

	AGA (n=32)	SGA (n=12)	LGA (n=6)
Hypertensive Disorders of Pregnancy	12 (38%)	7 (47%)	0 (0%)
Diabetes Mellitus	10 (31%)	1 (7%)	3 (50%)
Thyroid Disorders	6 (19%)	1 (7%)	2 (33%)
Maternal Mental Health Disorder*	8 (25%)	2 (14%)	0 (0%)
Immune Disorders**	2 (6%)	2 (14%)	1 (17%)

*Depression, anxiety, bipolar disease

**Crohn's disease, immune thrombocytopenic purpura, human immunodeficiency virus

Table 3: Fetal and placental volumes in high-risk pregnancies with appropriate-for-gestational age (AGA), small-for-gestational age (SGA), and large-for-gestational age (LGA) offspring

	AGA (n=32)	SGA (n=12)	LGA (n=6)
Placental Volume (cm^3)	665.1 ± 195.7	429.5 ± 200.4[1]	988.3 ± 384.2[1,2]
Fetal Body Volume (cm^3)	1527.5 ± 729.5	1063.1 ± 642.1	1738.5 ± 1122.4
Fetal Brain Volume (cm^3)	182.2 ± 78.9	167.7 ± 83.7	212.9 ± 107.9
Fetal Body: Fetal Brain Ratio	8.46 ± 1.05	6.88 ± 1.01[1]	8.07 ± 2.74[1]
Fetal Body: Placenta Ratio	2.22 ± 0.83	2.409 ± 1.14	1.59 ± 0.60[§]
Fetal Brain: Placenta Ratio	0.27 ± 0.09	0.37 ± 0.19[3]	0.21 ± 0.06

[1] Significantly different from AGA at $p < 0.001$

[2] Significantly different from SGA at $p < 0.001$

[3] Significantly different from AGA at $p = 0.019$

[§] $P = 0.089$

Figure 1. Placental volumes (panel A) and fete-placental ratios (panel B) across advancing gestational age.

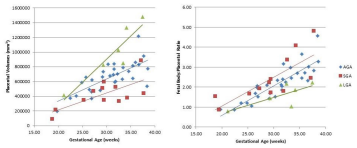

IMAGE CAPTION:

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