

GENERAL

Abstracts 1 – 8

Moderators: Kate Menard, MD, President, SMFM; George Saade, MD, Immediate Past President, SMFM; Michael Lu, MD, 2013 Honorary Member

**1 Pessaries in multiple pregnancy as a prevention of preterm birth (ProTWIN): a randomized controlled trial**

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**OBJECTIVE:** To evaluate whether prophylactic use of a cervical pessary can prevent preterm birth in women with a multiple pregnancy.

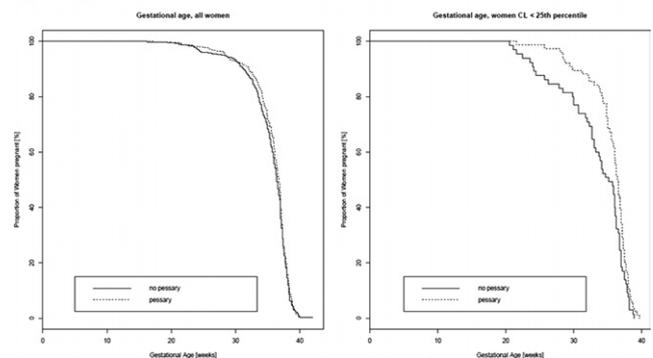
**STUDY DESIGN:** We performed a randomized trial in 40 hospitals in the Netherlands (ProTWIN NTR1858). Women with a multiple pregnancy were randomly assigned to a cervical pessary or no intervention. The primary outcome was a composite adverse neonatal outcome defined as PVL, IRDS, BPD, IVH II B or worse, NEC, proven sepsis or death before discharge. Secondary outcomes included time to delivery, and birth rates before 32 and 37 weeks. We performed a prespecified subgroup analysis for women with a CL < the 25th percentile at 16-20 weeks of gestation. We needed 800 women to show a reduction in the adverse neonatal outcome rate from 12.4% till 6.7%. Analysis was by intention to treat.

**RESULTS:** We allocated 403 women to the pessary group and 410 to no intervention, and as writing the abstract 97% of the outcome data are complete. There were 42 (11%) women in the pessary group and 42 (11%) in the control group who had at least one child with a composite adverse neonatal outcome (RR 1.0; CI 95% 0.67-1.5). A pessary did not significantly reduce the delivery rate < 32 weeks (9% vs 12%, RR 0.76; 0.50-1.1) or 37 weeks of gestation (54% vs 57%, RR 0.93; 0.82-1.0). However, in the prespecified subgroup of women with a CL < 25th percentile (38 mm), the pessary group (N=78) had a lower adverse neonatal outcome rate as compared the non-intervention group (N=65) (10% vs 25%, RR 0.41; 0.19-0.90). This was accompanied by

a significantly reduced preterm delivery rate <32 wk (12% vs 28%, RR 0.43; 0.21-0.89), but not <37 wk (61% vs 75%, RR 0.80; 0.54-1.2).

**CONCLUSION:** In an unselected population of women with a multiple pregnancy we found no proof for effectiveness of the use of a cervical pessary in the prevention of preterm birth. However, in women with a cervical length < the 25th percentile at 16-20 weeks, a pessary significantly reduced both adverse neonatal outcome and severe preterm birth rates.

Figure 1: Kaplan Meier curves for time to pregnancy for all women (left) and for the prespecified subgroup with a cervical length below 25th percentile (38 mm) (right).



**2 Multiple Courses of Antenatal Corticosteroids for preterm birth study: 5-year outcomes (MACS-5)**

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**OBJECTIVE:** Recent trials of repeated courses of antenatal corticosteroid therapy show some benefits in the reduction of respiratory distress but have raised concerns regarding potential harm. Long-term outcomes at 2 years of age have shown no benefit in the neurodevelopmental status of the children. The aim of this study was to determine the effects of repeated courses of antenatal corticosteroid therapy versus placebo on death or neurodevelopmental impairment among the children enrolled in the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) at 5 years of age.

**STUDY DESIGN:** The primary outcome was a combined outcome of death or survival with a severe disability in at least one of the following

domains: non-ambulatory cerebral palsy, blindness in at least one eye, deafness, need for visual or hearing aids, neuro-cognitive disability at 5 years of age. Five year follow-up was conducted from 2006-2012 in 52 of the initial 80 centers worldwide, where 2141 of 2304 fetuses/infants (93%) were enrolled. A total of 1728(80.7%) had adequate data for the main outcome at 5 years of age.

**RESULTS:** There was no significant difference between the two treatment groups in the risk of death or neurodevelopmental difficulty: 217 (24.9%) of the 873 in the repeat courses group vs. 210 (24.6%) of the 855 in the placebo group, [odds ratio 1.025, 95% confidence interval 0.81-1.29,  $p=0.83$ ]. The rates of death or individual neurodevelopmental difficulties did not differ significantly between the two groups.

**CONCLUSION:** Multiples courses of antenatal corticosteroid therapy given, every 14 days, do not increase or decrease the risk of death or neurodevelopmental difficulties by 5 years of age compared with a single course. Because there has been no clear benefit seen in the neonatal period, as well as at 2 and 5 years of age, this approach of antenatal corticosteroids is not recommended for routine use. Future research may be warranted for a more specified use of repeated courses of antenatal corticosteroids.

	Repeat N=873 N (%)	Placebo N=855 N (%)	OR [95% CI]	Level of Significance
Composite*	217 (24.9)	210 (24.6)	1.025 [0.81,1.29]	0.83
Death	46 (5.3)	47 (5.5)	0.95 [0.62,1.46]	0.82
Neuromotor	4 (0.004)	11 (0.01)	0.35 [0.11,1.11]	0.07
Neurosensory Blindness Visual aids Deafness Amplification	1 (0.1) 61 (7.4) 11 (1.3) 4 (0.5)	2 (0.3) 52 (6.4) 6 (0.7) 5 (0.6)	1.12 [0.77,1.63]	0.54
Neurocognitive** CBCL 1½-5 BRIEF-P	76 (9.2) 76 (9.2)	75 (9.3) 84 (10.4)	0.98 [0.73, 1.33]	0.92

\*Apart from a death, child may have more than 1 disability; \*\*10 cases were reviewed by an adjudication committee to determine whether they met the primary outcome; 5 cases were determined to have met the primary outcome.

### 3 Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial

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**OBJECTIVE:** To evaluate the use of 17 alpha-hydroxyprogesterone caproate (17P) to reduce the risk of preterm delivery in asymptomatic twin pregnancy with short cervix.

**STUDY DESIGN:** This open-label multicenter randomized controlled trial took place at 10 university hospitals between June 2006 and January 2010. Women older than 18 years and carrying twins were eligible between 24+0 through 31+6 weeks of gestation if they were asymptomatic, presented a cervical length less than 25 mm as measured by routine transvaginal ultrasound and provided a written informed consent. Women were randomly assigned in a 1:1 ratio to receive 500 mg of intramuscular 17P, and repeated twice a week until 36 weeks or preterm delivery, whichever occurred first, or to no treatment with 17P (control group). The primary outcome was time from randomization to delivery.

**RESULTS:** Maternal characteristics of the 82 women in the 17P group and the 83 women in the control group were similar. Outcome data

were available for 161 of the 165 women (97.6%). The intent-to-treat analysis with censoring at last follow up showed no significant difference between the 17P and controls group in median [Q1-Q3] time to delivery (45 [26-62] and 51 [36-66] days, respectively; mean difference, -7; 95% CI, -15; +1). Treatment with 17P was associated with a significantly increase in the rate of preterm deliveries before 32 weeks of gestation (29% vs 12%,  $p=0.007$ ), but not before 37 weeks of gestation (80% vs 77%,  $p=0.70$ ) or 34 weeks of gestation (44% vs 28%,  $p=0.10$ ). Median [Q1-Q3] birth weight did not differ between 17P and controls groups for twin 1 (2120 [1750-2471]g and 2215 [1982-2535] g,  $p=0.06$ ) but differ significantly for twin 2 (2090 [1540-2425] and 2230 [1985-2535] g,  $p=0.027$ ). There was a non significant trend to an increase of neonatal morbidity in a 17P group.

**CONCLUSION:** 17P is ineffective in women with asymptomatic twins and short cervix for prevention of preterm delivery and possibly harmful.

### 4 Antenatal origins of metabolic syndrome in fetuses of obese women

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**OBJECTIVE:** Molecular mechanisms that predispose offspring of obese pregnant women to insulin resistance, appetite dysregulation, and fatty liver disease are poorly understood. We sought to understand the effects of maternal obesity on fetal gene expression by analyzing cell-free fetal RNA (cffRNA) in amniotic fluid supernatant (AFS).

**STUDY DESIGN:** We prospectively studied cffRNA in AFS of women with singleton fetuses undergoing clinically indicated 2nd trimester genetic amniocenteses. Eight obese gravidas (Ob, BMI  $\geq 30$ ) and 8 lean controls (L, BMI  $< 25$ ) were matched for gestational age and fetal sex. Exclusion criteria included abnormal karyotype and structural anomalies. CffRNA was extracted, amplified, and hybridized to whole genome expression arrays. Genes significantly differentially regulated in 8/8 pairs were identified using paired t-test with the Benjamini-Hochberg (BH) correction. Functional analyses were performed using Ingenuity Pathways Analysis™ software. Genes and transcription factors associated with bias-corrected absolute Z-scores  $\geq 2.0$  or BH  $p < .05$  were called significant.

**RESULTS:** Demographic characteristics are shown in Table 1. There were 205 differentially regulated genes in fetuses of obese gravidas. The most up-regulated gene (9-fold) in Ob was *APOD*, which encodes a lipoprotein integral to lipid regulation, glucose metabolism, and inflammatory response. Upstream regulator analyses demonstrated significant activation of the estrogen receptor and the transcription factors *STAT3* and *FOS* in fetuses of obese women.

**CONCLUSION:** Expression of *APOD*, *STAT3*, and *FOS* is implicated in insulin resistance, hyperleptinemia, hepatic steatosis, atherosclerosis, toll-like receptor signaling, and inflammatory response. Analysis of cffRNA in AFS demonstrates a pro-estrogenic, pro-inflammatory milieu for fetuses of obese women. Molecular mechanisms predisposing offspring of obese women to metabolic complications may be initiated as early as the second trimester.

#### Subject demographics and array hybridization characteristics

	Obese	Lean	p-value
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	35 $\pm$ 3.3	21.9 $\pm$ 1.7	<0.001
Maternal age (yrs, mean $\pm$ SD)	37.1 $\pm$ 5	33.9 $\pm$ 5.5	0.21
Gestational age (wks, mean $\pm$ SD)	17.9 $\pm$ 1.7	18 $\pm$ 1.4	0.73
Fetal Sex (M:F)	4, 4	4, 4	N/A
Array Hybridization Efficiency	42.1 $\pm$ 3.5	41.9 $\pm$ 4.9	0.89

**5 Should routine controlled cord traction be part of the active management of third stage of labor? The Tracor multicenter randomized controlled trial**

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**OBJECTIVE:** Active management of the third stage of labor is recommended for preventing postpartum hemorrhage (PPH). However, the specific effects of each of its components have not been adequately evaluated. The TRACOR Study aimed to assess the impact of controlled cord traction on the incidence of PPH and other characteristics of the third stage of labor, in a high-resource setting.

**STUDY DESIGN:** Randomized controlled trial conducted between 01/2010 and 01/2011 in 5 French university hospitals. 4058 women aged ≥18, with a planned vaginal delivery, at a gestational age ≥35 weeks, with a singleton fetus were randomly assigned to have third stage of labor managed either by controlled cord traction (CCT) or by standard placenta expulsion (SPE) i.e. awaiting the spontaneous placental separation before facilitating its expulsion. Prophylactic oxytocin just after birth was administered in the 2 arms. The primary outcome was the incidence of PPH ≥500 mL as measured in a collector bag.

**RESULTS:** The incidence of PPH was not different in the CCT (9.8% (196/2005) and in the SPE (10.3% (206/2008) groups, RR 0.95, 95% CI (0.79 to 1.15). The need for manual removal of placenta was significantly less frequent in the CCT than in the SPE group (4.2% (85/2033) and 6.1% (123/2024), RR 0.69, 95% CI (0.53 to 0.90)); as was third stage > 15 min (4.5% (91/2030) and 14.3% (289/2020), RR 0.31, 95% CI 0.25 to 0.39). Women in the CCT group reported a significantly lower intensity of pain and discomfort during the third stage than those in the SPE group. No uterine inversion occurred in either arm.

**CONCLUSION:** Controlled cord traction does not decrease the incidence of PPH. However, in hospital settings where deliveries are managed by trained clinicians, the benefit/harm balance of controlled cord traction is in favor of its integration in routine practice as it is safe and results in shorter duration of third stage, less need for manual removal of placenta, and higher satisfaction of women.

**Main outcomes**

	Controlled Cord Traction	Standard Placenta Expulsion	Risk ratio (95% CI)	Mean difference (95% CI)
Blood loss ≥ 500mL	196/2005 (9.8)	206/2008 (10.3)	0.95 (0.79-1.15)	/
Total blood loss (mL) (mean (SD) (n))	207.3 (5.1) (2005)	216.7 (6.0) (2008)	/	-9.4 (-24.8;6.0)
Blood transfusion for PPH	12/2034 (0.6)	9/2024 (0.4)	1.33 (0.56-3.14)	/
Arterial embolization/surgery for PPH	3/2034 (0.1)	5/2024 (0.3)	0.60 (0.14-2.49)	/
Peripartum change in Hb*(g/dL) (mean (SD) (n))	0.86 (0.03) (1961)	0.87 (0.03) (1953)	/	-0.02 (-0.10;0.07)
Peripartum change in Ht* (%) (mean (SD) (n))	2.14 (0.09) (1904)	2.19 (0.09) (1890)	/	-0.05 (-0.29;0.19)
Duration of third stage (min) (mean (SD) (n))	5.46 (0.11) (2030)	8.72 (0.15) (2020)	/	-3.26 (-3.62; -2.90)
Third stage ≥ 15 min	91/2030 (4.5)	289/2020 (14.3)	0.31 (0.25-0.39)	/
Manual removal of placenta	85/2033 (4.2)	123/2024 (6.1)	0.69 (0.53-0.90)	/
Additional uterotonics after placenta delivery	727/2030 (35.8)	805/2024 (39.8)	0.92 (0.83-0.97)	/
Maternal pain during 3rd stage	109/1892 (5.8)	138/1868 (7.4)	0.78 (0.61-0.99)	/
Cord rupture	89/2034 (4.4)	2/2024 (0.1)	44.3 (10.9-179.6)	/

Data are n/N (%) unless otherwise stated.

\* Peripartum Hb and Ht measured within 8th month of gestation and arrival in labor ward; postpartum Hb and Ht measured at Day 2 postpartum.

**6 Cervical funneling or intraamniotic debris and preterm birth in nulliparous women with short cervix**

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**OBJECTIVE:** To evaluate whether the presence of cervical funneling or intra-amniotic debris is associated with higher rates of preterm birth (PTB) in asymptomatic nulliparous women with a short cervical length (CL).

**STUDY DESIGN:** Secondary analysis of a multicenter trial of women between 16 and 22 weeks with a singleton gestation and a CL <30 mm on transvaginal ultrasound randomized to either 17 hydroxyprogesterone caproate (17-OHPc) or placebo. Sonographers were centrally certified in CL measurement, as well as identification of intra-amniotic debris and cervical funneling (with measurement of the funnel if present). Univariable and multivariable analyses were performed.

**RESULTS:** Of the 657 randomized patients, 157 (24%) had funneling, 78 (12%) had debris, and 45 (7%) had both on the screening ultrasound. Women with either of these findings were older (22.7 vs. 22.0 mean years, p=0.03), had a higher pre-pregnancy body mass index (27.6 vs. 25.0 kg/m<sup>2</sup>, p<0.001) and a lower CL (19.5 vs. 25.6 mm, p<0.001) than those without these findings. PTB < 37 wks was higher for women with a funnel (2.2 OR, 95% CI 1.5-3.3) or debris (1.7 OR, 95% CI 1.0-2.9). Results were similar for progressively earlier preterm delivery (Table). The associations persisted when controlling for 17-OHPc administration, but not after adjusting for CL, except in the case of debris and delivery prior to 35, 34, or 32 weeks. Preterm birth was also associated with the length of the funnel, but was no longer significant after controlling for CL.

**CONCLUSION:** The presence of cervical funneling is not independently associated with preterm birth in nulliparous women with a short cervix. However, the presence of intra-amniotic debris increases the risk of early preterm birth (<35 wk) independently of the cervical length.

Outcome	Univariable OR (95% CI)	Multivariable OR (95% CI)
<b>Funnel</b>		
PTB <37 wks	2.2 (1.5-3.3)	1.1 (0.7-1.8)
PTB <35 wks	2.8 (1.8-4.4)	1.3 (0.7-2.4)
PTB <34 wks	2.8 (1.8-4.5)	1.4 (0.8-2.5)
PTB <32 wks	3.7 (2.1-6.4)	1.6 (0.8-3.2)
<b>Debris</b>		
PTB <37 wks	1.7 (1.0-2.9)	1.1 (0.6-1.9)
PTB <35 wks	3.1 (1.8-5.2)	1.9 (1.0-3.4)
PTB <34 wks	3.3 (1.9-5.6)	2.0 (1.1-3.7)
PTB <32 wks	5.1 (2.8-9.2)	3.1 (1.6-5.9)

**7 The Twin Birth Study: a multicenter RCT of planned cesarean section (CS) and planned vaginal birth (VB) for twin pregnancies 320 to 386/7 weeks**

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**OBJECTIVE:** To compare planned CS with planned VB for twins 320/7 to 386/7 weeks, if the first twin is cephalic.

**STUDY DESIGN:** Prospective RCT. Eligibility: Twins 32 to 38+6weeks, live fetuses, Twin A cephalic, EFW 1500g- 4000g. Exclusion: Fetal

reduction at >13 wks gestation, lethal fetal anomaly, contraindication to labour. Delivery planned between 375/7 to 386/7 weeks by CS or inducing labour. Primary composite outcome: perinatal/neonatal mortality and/or serious neonatal morbidity. 2800 patients required to detect reduction of primary outcome from 4% to 2%. power 80%, 2-sided,  $\alpha$  error of 0.05. A logistic model was used with generalized estimating equations to account for correlation between babies from the same pregnancy.

**RESULTS:** 2804 women randomized from 26 countries. 1398 to planned CS vs.1406 to planned VB. There was no significant difference between treatment groups. Fifty seven babies of 2781(2.05%) experienced the primary outcome in planned CS vs.52 (1.87%) in planned VB (OR1.098,CI 0.726 -1.663,p = 0.6569). There was no significant interaction between treatment group and parity, GA at randomization, mother's age, presentation of twin B, Chorionicity, and country's PNMR.Twin B more likely to experience the primary outcome (OR=1.895,CI:1.329-2.703, p=0.0003). The interaction between treatment group and birth order was not significant (OR;A=1.239; OR;B=1.030, p=0.6125). 89 9% of the women who planned CS delivered both babies by CS. 60.45% in planned VB delivered at least twin A vaginally. 4% of women in planned VB group delivered twin B by CS following VB of twin A. Women in the planned CS delivered earlier but had no increase in maternal mortality or morbidity compared to planned VB.

**CONCLUSION:** Planned CS in twins at 32-38 week does not decrease (or increase) perinatal/neonatal death or serious neonatal morbidity vs planned VB when the first twin is cephalic.

## 8 Whole metagenomic shotgun sequencing reveals a vibrant placental microbiome harboring metabolic function

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**OBJECTIVE:** Humans and our microbiota have co-evolved as a metabolic and antigenic commune ("microbiome") with a collective genome ("metagenome") which retains body site-specific niches. To date, the human placental microbiome has yet to be robustly interrogated. Since the placenta harbors diverse metabolic and immune regulatory functions, it is unlikely to be "sterile" and is likely a unique microbiome niche. Our aim was to leverage our developed Human Microbiome Project pipelines to identify community membership (placental microbiome) and function (metagenomic carriage of metabolic pathways).

**STUDY DESIGN:** In a strictly matched-cohort design, placentas (n 12) were rigorously sterile collected from term gravidae and stratified by presence or absence of remote antenatal infection (e.g., uncomplicated UTI). Genomic DNA was extracted (MoBIO), and metagenomic libraries were subjected to shotgun sequencing (WGS; Illumina). Host (human) DNA was filter binned, and microbial DNA was analyzed with MG\_RAST (taxonomic abundance) and HuMAaN (metabolic pathway reconstruction).

**RESULTS:** >200 million reads (>36 gigabytes) of WGS data were generated, and 357 megabytes of binned microbial data was analyzed. In total, the placental microbiome comprised of 728 species (from among 329 genus). From the 65 most abundant genus, robust metabolic reconstruction revealed 2413 encoded prokaryotic genes. Antenatal infection significantly increased abundance, diversity, and richness of genus (LDA effect size>4, A), resulting in distinct functional metabolic pathways (B,C). The placental microbiome was not significantly structured by maternal BMI> 30 nor mode of delivery.

**CONCLUSION:** Metagenomic sequencing reveals for the first time that there exists a vibrant and functional placental microbiome community which is structured by a remote history of maternal antenatal infection. We speculate that the placental microbiome likely contributes to both its metabolic and immune functions, and is essential to human reproduction.

### Metagenomics of the human placental microbiome

