OC001—A PROMISING PREDICTOR FOR HEART DISEASES AND DIURETIC DRUG THERAPY IN THE ALDOSTERONE RECEPTOR GENE

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Introduction: Aldosterone mediates sodium and water retention in hypovolemia. In normovolemia, aldosterone primarily mediates kaliuresis. To mediate kaliuresis, aldosterone downregulates the sodium chloride cotransporters NCC and up-regulates the epithelial sodium channel ENaC. NCC downregulation increases sodium chloride transport to ENaC, where it is reabsorbed in turn for potassium, which is then excreted. We investigated whether kaliuresis is associated with the aldosterone receptor polymorphism rs3857080 in normovolemic healthy volunteers.

Patients (or Materials) and Methods: We genotyped 195 healthy young men for rs3858070. In a triple-crossover study, 101 of them had ingested a sodium-chloride restricted diet 3 times for each a diet run-in day, a second diet day and a third diet plus verum day. Verums were 25-mg hydrochlorothiazide (HCT), 100-mg HCT and 200-mg triamterene. In a second triple-crossover study, 94 men took single oral doses of bumetanide (2 mg), furosemide (80 mg), and torsemide (10 mg). To avoid hypovolemia, the subjects were repetitively encouraged to drink in both studies.

Results: Potassium excretion was in both studies associated with rs3857080, which had a minor allele frequency of 0.111. Comparatively high potassium excretion was associated with the minor A-allele under most conditions (Table). After torsemide, which is a loop diuretic such as bumetanide and furosemide but in addition blocks the aldosterone receptor, potassium excretion was similar between the A- and the G-allele of rs3857080.

Table. Urinary potassium excretion over 24 hours and rs3857080.

	A/A	G/G
NaCl restriction	3.7 (0.2)[*]	2.8 (0.1)
HCT 25 mg	4.8 (0.6)	3.7 (0.1)
HCT 100 mg	5.5 (0.6)	4.1 (0.1)
Triamterene	3.3 (0.5)	2.2 (0.1)
Bumetanide	3.5 (0.3)	2.8 (0.1)
Furosemide	3.5 (0.3)	3.1 (0.1)
Torsemide	2.5 (0.3)	2.6 (0.1)

[*]Mean (SEM) of gram amounts normalized to 120 mL/min creatinine clearance.

Conclusion: Taken together, our findings indicate that the A-allele of rs3857080 marks a comparatively active aldosterone receptor. Carriers of the A-allele may be prone to hypokalemia and its devastating consequences. The A-allele of rs3857080 may predict less optimal outcome of diuretic therapy and of heart diseases. Antialdosteronergic drugs such as spironolactone, eplerenone, and torsemide may be especially indicated in carriers of the A-allele. In consequence, rs3857080 is a highly promising candidate for in vitro studies as well as for clinical research.

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OC002—CYP2R1 GENETIC POLYMORPHISMS ARE ASSOCIATED WITH LOWER 25-HYDROXY VITAMIN D LEVELS IN LEBANESE SUBJECTS

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Introduction: Despite plentiful sunshine in the Middle East, populations in general, and in Lebanon in particular, have some of the lowest levels of 25-hydroxy vitamin D (25-OHD) worldwide. Our group has demonstrated such findings across the lifespan; predictors include gender, season, and clothing style (http://staff.aub.edu.lb/~webcmop/publications.html). However, the possibility of an underlying genetic modulation of circulating 25-OHD levels remains unexplored. 25-Hydroxylation is mainly driven by cytochrome P-450 2R1 (CYP2R1) drug metabolizing enzyme; we therefore hypothesized that carriage of *CYP2R1* single nucleotide polymorphisms (SNPs) may be associated with variability in 25-OHD levels.

Patients (or Materials) and Methods: Baseline 25-OHD levels were obtained for 172 elderly Lebanese patients: 60% female; age, 70.9 (4.3) (mean [SD]) years; BMI, 30.3 (4.8) kg/m^2; with vitamin D, 25-OHD, 18.7 (7.9) ng/mL. Genotyping was performed for 4 functionally important SNPs (rs12794714, rs10741657, rs1562902, and rs10766197) in *CYP2R1* gene by using real-time PCR. Means were first compared with univariate analysis, and then multivariate regression analysis was run adjusting for age, gender, BMI, and season.

Results: Minor allele frequencies were 0.50, 0.29, 0.36, and 0.49 for rs12794714, rs10741657, rs1562902, and rs10766197, respectively; proportions comparable to those reported in Caucasian populations. Univariate analysis showed that carriers of the rs12794714 and rs10766197 variant alleles are associated with baseline 25-OHD that was 3.24 ng/mL and 4.48 ng/mL lower, respectively ($P = 0.018$ and 0.004). This significant association remained for rs10766197 after adjusting for covariates ($\beta = -6.401$ [95% CI, −11.775 to −1.027]; $P = 0.020$).

Conclusion: This is the first study that shows the association of genetic polymorphisms in *CYP2R1* with hypovitaminosis D in the Middle East. Further analysis is ongoing to evaluate the effect of these SNPs on 25-OHD levels achieved after supplementation with different doses of vitamin D.

Disclosure of Interest: None declared.

OC003—PREGNANCY OUTCOME FOLLOWING MATERNAL EXPOSURE TO MIRTAZAPINE: PRELIMINARY RESULTS OF A COLLABORATIVE ENTIS STUDY

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Introduction: Mirtazapine is a noradrenergic and serotonergic antidepressant mainly acting through blockade of presynaptic **alpha-2** receptors. Published data on pregnancy outcome after exposure to mirtazapine are scarce. This study addresses the risk associated with exposure to mirtazapine during pregnancy.

Patients (or Materials) and Methods: Multicenter (n = 11), observational prospective cohort study comparing pregnancy outcomes after exposure to mirtazapine with 2 matched control groups: exposure to any selective serotonin reuptake inhibitor (SSRI) as a disease-matched control group, and general controls with no exposure to medication known to be teratogenic or to any antidepressant. Data were collected by members of the European Network of Teratology Information Services (ENTIS) during individual risk counseling between 1995 and 2011. Standardized procedures for data collection were used in each center.

Results: A total of 357 pregnant women exposed to mirtazapine at any time during pregnancy were included in the study and compared with 357 pregnancies from each control group. The rate of major birth defects between the mirtazapine and the SSRI group did not differ significantly (4.5% vs 4.2%; unadjusted odds ratio, 1.1; 95% confidence interval, 0.5–2.3, $P = 0.9$). A trend toward a higher rate of birth defects in the mirtazapine group compared with general controls did not reach statistical significance (4.2% vs 1.9%; OR, 2.4; 95% CI, 0.9–6.3; $P = 0.08$). The crude rate of spontaneous abortions did not differ significantly between the mirtazapine, the SSRI, and the general control groups (9.5% vs 10.4% vs 8.4%; $P = 0.67$), neither did the rate of deliveries resulting in live births (79.6% vs 84.3% in both control groups; $P = 0.15$). However, a higher rate of elective pregnancy-termination was observed in the mirtazapine group compared with SSRI and general controls (7.8% vs 3.4% vs 5.6%; $P = 0.03$). Premature birth (<37 weeks) (10.6% vs 10.1% vs 7.5%; $P = 0.38$), gestational age at birth (median, 39 weeks; interquartile range (IQR), 38–40 in all groups; $P = 0.29$), and birth weight (median, 3320 g; IQR, 2979–3636 vs 3230 g; IQR, 2910–3629 vs 3338 g; IQR, 2967–3650; $P = 0.34$) did not differ significantly between the groups.

Conclusion: This study did not observe a statistically significant difference in the rate of major birth defects between mirtazapine, SSRI-exposed, and nonexposed pregnancies. A slightly higher rate of birth defects was, however, observed in the mirtazapine and SSRI groups compared with the low rate of birth defects in our general controls. Overall, the pregnancy outcome after mirtazapine exposure in this study is very similar to that of the SSRI-exposed control group.

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OC004—FETAL EXPOSURE TO NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAID) AND SPONTANEOUS ABORTIONS

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Introduction: Spontaneous abortions are the most common complication of pregnancy and nonsteroidal anti-inflammatory drugs (NSAID) are among the most widely used groups of drugs during the first trimester of pregnancy. Published data are inconsistent regarding the risk for spontaneous abortions after exposure to NSAID.

Patients (or Materials) and Methods: A population-based retrospective cohort study was conducted including all women who conceived between January 2003 and December 2009 and admitted for birth or diagnosed with spontaneous abortion at Soroka Medical Center, Clalit Health Services, Israel. A computerized database of medication dispension was linked with 2 computerized databases containing information on births and spontaneous abortions. Time-varying COX regression models were constructed adjusting for mother's age, diabetes mellitus, hypothyroidism, hypercoagulable or inflammatory conditions, history of recurrent miscarriages, presence of intrauterine contraceptive device, ethnicity, and self-reporting tobacco use during pregnancy and the year of pregnancy.

Results: There were 65,457 women who conceived during the study period and admitted at SMC: 58,949 (90.1%) for birth and 6508 (9.9%) for spontaneous abortion. A total of 4495 (6.9%) pregnant women were exposed to NSAID during the study period. Exposure to NSAID was not an independent risk factor for spontaneous abortion as groups (adjusted hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.97–1.20 and adjusted HR, 1.67; 95% CI 0.95–2.95 for nonselective and selective COX2 inhibitors, respectively) or as specific drugs. Additionally, no dose response effect was found.

Conclusion: In this large population-based retrospective cohort study, no increased risk for spontaneous abortions was found following exposure to NSAID Table.

Table. The unadjusted and adjusted risk (hazard ratios and 95% CI) for spontaneous abortion following exposure to NSAID: results from time-varying multivariate Cox regression models.

	Spontaneous Abortions Hazard Ratio (95% CI)	
	Unadjusted	**Adjusted***
Nonselective COX inhibitors	1.13 (1.01–1.25)	1.08 (0.97–1.20)
Ibuprofen	1.13 (0.98–1.30)	1.05 (0.92–1.21)
Diclofenac	1.21 (0.98–1.48)	1.19 (0.97–1.47)
Indomethacin	3.54 (2.20–5.71)	3.33 (2.06–5.36)
Naproxen	1.87 (0.66–1.17)	0.88 (0.66–1.18)
Etodolac	1.26 (0.88 –1.80)	0.14 (0.8–1.64)
COX2 selective inhibitors	1.97 (1.12–3.47)	1.67 (0.95–2.95)

Disclosure of Interest: None declared.

OC005—BIASES ON THE ADMINISTERED PARENTERAL DOSES OF AN EXPERIMENTAL DRUG DURING PHASE I CLINICAL TRIALS

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Introduction: The pharmaceutical aspects of drug administration in clinical trials receive poor consideration compared with the important attention devoted to the analytical and mathematical aspects