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Urinary organophosphate metabolite levels in Palestinian pregnant women: results of the Middle East Regional Cooperation Project

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The purpose of the study was to measure urinary organophosphate (OP) metabolites in Palestinian pregnant women, and to compare levels with those in pregnant women in Jerusalem and women from the general population in Israel. We measured six dialkyl phosphates in urine samples collected from 148 pregnant women from the West Bank area. Median total dimethyl phosphate (DM_{total}) levels were significantly lower in Palestinian women compared to Jerusalem pregnant women and women in Israel ($p = 0.041$). In Palestinian women reporting that their place of residence was near an agricultural field, DM_{total} levels were significantly higher ($p = 0.037$). Lower urinary excretion of dimethyl phosphate pesticide metabolites in Palestinian women compared to Israeli women may result from lower consumption of fruits and vegetables in the Palestinian population. Our findings highlight differences in OP pesticide exposure in populations with close geographical proximity but with differences in culture, diet, lifestyle, and regulatory oversight of pesticides.

Keywords: organophosphates; pesticides; maternal; pregnant; biomonitoring; exposure

Introduction

The developing fetus is uniquely vulnerable to the effects of organophosphate (OP) pesticides. Prenatal exposure to OP pesticides is associated with decreased birth weight (Whyatt et al. 2004), abnormal reflexes in newborns (Young et al. 2005; Engel et al. 2007), lower scores on tests of cognitive and motor development (Rauh et al. 2006), increased risk of pervasive developmental problems (Eskenazi et al. 2007), a significant reduction in childhood IQ (Bouchard et al. 2011; Engel et al. 2011; Rauh et al. 2011), brain anomalies (Rauh et al. 2012), autism spectrum disorders (Shelton et al. 2014), and respiratory symptoms consistent with possible asthma in childhood (Raanan et al. 2015). Since prenatal exposure to OPs can increase the risk of adverse birth effects, neurodevelopmental outcomes, and respiratory symptoms, it is important to investigate maternal exposure to these pesticides during pregnancy.

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While data are available on maternal exposure to OP pesticides during pregnancy in many international populations, including the USA, the Netherlands, Israel, China, Thailand, and Mexico (Ye et al. 2009; Castorina et al. 2010; Fortenberry et al. 2014; Kongtip et al. 2014; Zhang et al. 2014), data on levels of exposure in Palestinian pregnant women are lacking. Previous studies in Israel have shown that pregnant women and the general population have relatively high levels of exposure to OP pesticides, especially those which metabolize to dimethyl phosphate (DM_{total}). Levels of these metabolites were almost 10 times higher in the general population in Israel than in US adults and almost three times higher than in Canadian adults, while in Israeli pregnant women DM metabolite concentrations were between four and six times higher than in pregnant women in the USA (Berman et al. 2011, 2013b).

Previous reports have indicated potentially high exposures to pesticides in Palestine from numerous pathways, including occupational and take-home exposure, ambient exposure from agricultural drift, and dietary exposure to pesticide residues. Issa et al. reported that illegal use of restricted or banned pesticides is common in the West Bank, as are practices that potentially increase exposures of farmers' family members (Issa et al. 2010). Five of fifteen pesticides reported by West Bank farmers as commonly used in 2006 were OP pesticides (azinphos-methyl, chlorpyrifos, dichlorvos, dimethoate, and methamidiphos). Pesticide poisoning is a major health problem in Palestine, and one third of pesticide poisoning cases in 2006–2010 had symptoms consistent with organophosphate poisoning (Sawalha et al. 2012). In a study on exposure of farmers and their families in the Nablus district, household dust samples contained detectable levels of both chlorpyrifos and methamidiphos (Abdel Raouf Al Faris, 2007). The reported lack of enforcement of good agricultural practices and sporadic reports of high residue levels in agricultural produce exported from Palestine also suggest that the Palestinian population may be highly exposed to pesticides (Al Sa"ed et al. 2011).

In this study, we present data on urinary concentrations of OP pesticides in pregnant women from Palestine. We compared levels in this cohort to the Israeli population in order to better understand the impact of dietary and environmental factors in Palestine on levels of exposure to OP pesticides.

Methods

Enrollment

In 2010–2012, one hundred and forty-eight women were recruited at prenatal clinics and hospitals in the West Bank (Nablus, Jenin, Hebron, Jericho, and Bethlehem) and the Red Crescent Hospital in East Jerusalem (Figure 1). The institutional review board at Al-Quds University approved the study. Women were eligible if they were in week 24–28 of a singleton pregnancy and had not developed a pregnancy complication (i.e. gestational diabetes, hypertension, and preeclampsia). At the time of recruitment, women were asked to provide one spot urine sample for analysis of dialkyl phosphate (DAP) metabolites, and complete a guided questionnaire. Participation was voluntary, and written-informed consent was obtained from all the women in the study.

Questionnaire

A trained interviewer administered a brief questionnaire to each woman. Information was obtained on occupation, partner's occupation, current and past agricultural work,

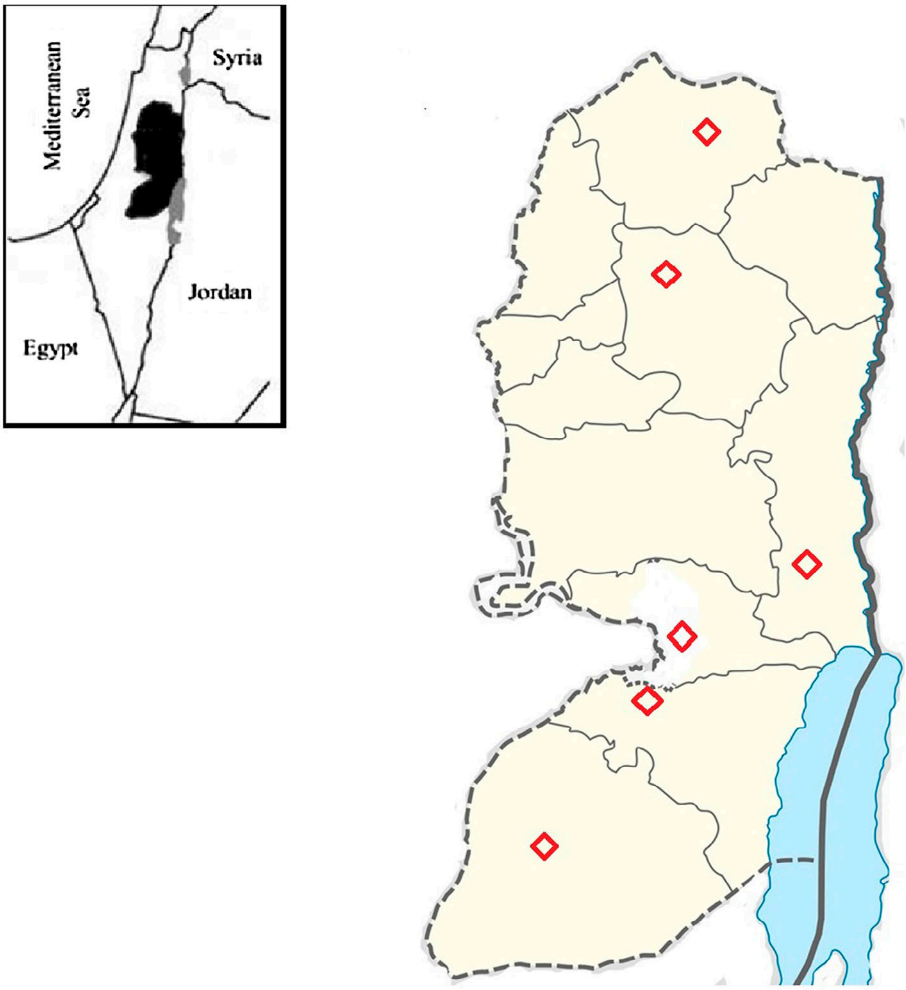

Figure 1. (Color online) Recruitment locations for pregnant Palestinian women.

education, smoking habits, parity, housing, distance between the residence and agricultural fields, and household use of pesticides.

Urine collection

Spot urine samples were collected in 120 mL urine specimen containers at the time of interview. All urine samples were maintained at 4 °C until they were frozen at − 20 °C. Urine samples were shipped to the University of Erlangen-Nuremberg in Germany on dry ice (− 70 °C), where they were analyzed.

Sample analysis

Laboratory analyses of DAP urinary concentrations and creatinine were performed at the Institute and Outpatient Clinic of Occupational, Social and Environmental

Medicine, University Erlangen-Nuremberg in Germany. Urinary concentrations of dimethylphosphate (DMP), diethylphosphate (DEP), dimethylthiophosphate (DMTP), diethylthiophosphate (DETP), dimethyldithiophosphate (DMDTP), and diethyldithiophosphate (DEDTP) were determined using a GC–MS/MS procedure (Barr et al. 2010). Isotope-labeled analogs of the analytes were added to the urine, which was then freeze-dried. The lyophilized urine was extracted with diethyl ether and acetonitrile. Next, the analytes were derivatized with pentafluorobenzyl bromide. After addition of water, liquid–liquid extraction was carried out twice with hexane to separate the derivatives from matrix components and excess of derivatization agent. Thereafter, GC–MS/MS analysis took place. Calibration was performed with standard solutions prepared in pooled urine. The limit of detection (LOD) ranged from 0.01 µg/L for DEDTP to 0.1 µg/L for DEP, DETP, DMP, and DMTP, and the limit of quantification (LOQ) ranged from 0.03 µg/L for DEDTP to 0.3 µg/L for DEP, DETP, DMP, and DMTP. Creatinine in urine was determined according to the Jaffé method (Larsen 1972). Quality assessment of the analytical procedures was performed by analyzing quality control samples and recording in quality control charts as well as by successful participation in proficiency tests of the German External Quality Assessment Scheme for both DAP analyses and creatinine (Göen et al. 2012).

Data analysis

Concentrations below the LOQ but above LOD for an analyte were replaced by the LOD for that analyte, and concentrations below the LOD were replaced with the LOD divided by the square root of 2 according to the statistical model by Hornung and Reed (1990). We calculated geometric means and percentiles (50th, 75th, 90th, and 95th) and their confidence intervals for urinary OP metabolite concentrations and for creatinine-adjusted concentrations. We calculated Spearman correlation coefficients between individual metabolites.

We used independent samples medians test, as well as independent samples Kolmogorov–Smirnov test, to compare differences in metabolite concentrations between the Palestinian cohort and two additional study populations: 120 females from the 2011 Israel Biomonitoring Study (IBS) (Berman et al. 2013a) and a subset of 73 pregnant women in Jerusalem participating in a study on exposure of pregnant women and their offspring to endocrine disrupting chemicals and organophosphate pesticides. In both the IBS and Jerusalem pregnant women study, spot urine samples were collected. Jerusalem pregnant women provided the urine sample during weeks 11–18 of pregnancy. We compared data on levels of creatinine adjusted and unadjusted DAP metabolites (µg/L, µg/g), as well as DM_{total}, sum of diethyl phosphate species (DE_{total}) and total DAP concentrations (µmol/L, µmol/g).

Within the Palestinian cohort, we used ANOVA to study associations between urinary DAP concentrations and potential predictors of exposure such as husband's work in agriculture and residence near agricultural fields.

Results

The mean age of the Palestinian pregnant women was 28 years (range 16–43) and the mean duration of gestation at recruitment was 27 weeks (range 21–34). Thirty-nine percent of Palestinian women had less than a high school level education, while twenty-five percent had a higher (bachelor's) degree. Most of the women (86 %) reported their profession as housekeeping. Five women (3 %) reported current work in agriculture while 27 (19 %) reported past work in agriculture. Seven women reported their husband's occupation as farmer. Forty-two (28 %) reported that a family member currently works in agriculture and an additional 13 (9 %) reported that family member worked in agriculture in the past. Thirty-seven women (25 %) reported that their place of residence was near an agricultural field, with reported distance ranging from 2 to 200 m.

Table 1 presents demographic characteristics of pregnant Palestinian women in the current study and those of pregnant women from Jerusalem and females in the 2011 IBS. Palestinian pregnant women were generally younger and less educated compared to Jerusalem pregnant women and females in the IBS.

Urinary OP pesticide concentrations

Geometric mean concentrations were highest for DMP and DMTP, followed by DEP and DETP. The strongest correlations were found between DMTP and DMDTP ($r = 0.812$) and between DEP and DETP ($r = 0.830$).

Within the Palestinian cohort, current ($n = 5$) or past work in agriculture ($n = 27$), husband's occupation as farmer ($n = 7$), and family member's occupation as farmer ($n = 42$) was not associated with increased metabolite levels. In 37 women reporting that their place of residence was near an agricultural field, geometric mean DMP levels were significantly higher ($p = 0.037$ when comparing creatinine adjusted values; $p = 0.084$ when comparing unadjusted values; $p = 0.024$ when comparing the distribution of results using the independent samples Kolmogorov–Smirnov test).

Comparison with Israeli populations

Geometric mean concentrations of DMP and DMTP metabolites were lower in Palestinian pregnant women compared to those in Jerusalem pregnant women and women in the IBS (Table 2). When comparing median values, DM_{total} levels were significantly lower in Palestinian women (0.13 µmol/L compared to 0.19 µmol/L in

Table 1. Demographic characteristics of Palestinian pregnant women, Israeli pregnant women, and females in the Israel Biomonitoring Study (IBS).

	Palestinian pregnant women ($n = 148$)	Jerusalem pregnant women ($n = 72$)	Females, Israel biomonitoring study ($n = 120$)
Age (mean) ± SD	28.2 ± 6.7	31.15 ± 4.8	40.9 ± 13.4
Education (%)			
< High school	39	0	23
High school	35	24	48
Higher education	25	76	27
Marital status (% married)	100	100	53
Smoking (%)	4[a]	3[b]	27

[a]Pregnant women were asked if they smoked prior to pregnancy.
[b]Pregnant women were asked if they currently smoke.

Table 2. Urinary concentrations of organophosphate pesticide metabolites in Palestinian pregnant women (PA) ($n = 148$), Jerusalem pregnant women (JR) ($n = 72$), and women in the IBS ($n = 120$).

		% > LOQ	Geometric mean	Percentile 50th	Percentile 95th	Percentile Maximum
DMP (μg/L)	PA	89.7	3.7	4.9	41.5	203.3
	JR	100	10.3	12.1	67.7	247.8
	IBS	100	14.4	14.9	69.9	116.5
DMTP (μg/L)	PA	97.2	8.6	8.6	84.9	1523.1
	JR	100	12.7	9.9	113.5	452.8
	IBS	100	9.5	8.7	152.2	246.3
DMDTP (μg/L)	PA	69.0	0.4	0.4	9.3	314.3
	JR	57	0.5	0.3	9.3	27.8
	IBS	74.2	0.4	0.3	8.7	41.9
DEP (μg/L)	PA	98.6	2.9	2.70	37.9	205.6
	JR	94.5	2.7	2.9	16.2	49.3
	IBS	98.3	2.1	2.2	8.6	13.5
DETP (μg/L)	PA	71.7	0.9	0.8	12.7	52.1
	JR	75.3	0.6	0.6	5.5	11.8
	IBS	76.7	0.5	0.5	3.3	5.4
DEDTP (μg/L)	PA	42.8	0.02	0.01	0.2	2.8
	JR	60	0.09	0.1	1.5	2.5
	IBS	40.8	0.03	0.01	0.2	1.8
Total DM (μmol/L)	PA	–	0.116	0.127	0.910	14.32
	JR	–	0.194	0.190	1.448	4.010
	IBS	–	0.206	0.200	1.829	2.600
Total DE (μmol/L)	PA	–	0.028	0.027	0.524	1.34
	JR	–	0.028	0.028	0.151	0.33
	IBS	–	0.020	0.022	0.077	0.11
Total DAPs (μmol/L)	PA	–	0.178	0.192	1.43	14.6
	JR	–	0.234	0.231	1.51	4.09
	IBS	–	0.231	0.220	1.84	2.72

Jerusalem pregnant women and 0.20 μmol/L in women in IBS, $p = 0.041$). In contrast, for DE_{total}, 95th percentile levels were higher in Palestinian pregnant women (Figures 2 and 3). Using the independent sample Kolmogorov–Smirnov test, distribution of results between Palestinian pregnant women and women in the IBS was significantly different for DM_{total} and total DAPs ($p < 0.001$, and $p = 0.01$, respectively), and different by trend for DE_{total} ($p = 0.066$). Results were comparable when comparing creatinine adjusted values.

Discussion

The results of the current study show that pregnant women in Palestine have lower DAP levels and DM_{total} levels compared to pregnant women in Jerusalem and women from the general population in Israel. Sample analyses for the current study and for the studies in the Israeli populations were conducted at the same laboratory, so differences in the reported concentrations are not the result of analytical uncertainty. These findings are surprising in light of previous reports on overuse, para-occupational exposures, and lack of regulatory oversight on pesticide use in Palestine (Issa et al. 2010; Al-Sa"ed et al. 2011) and the fact that 25 % of women in this rural cohort reported living near

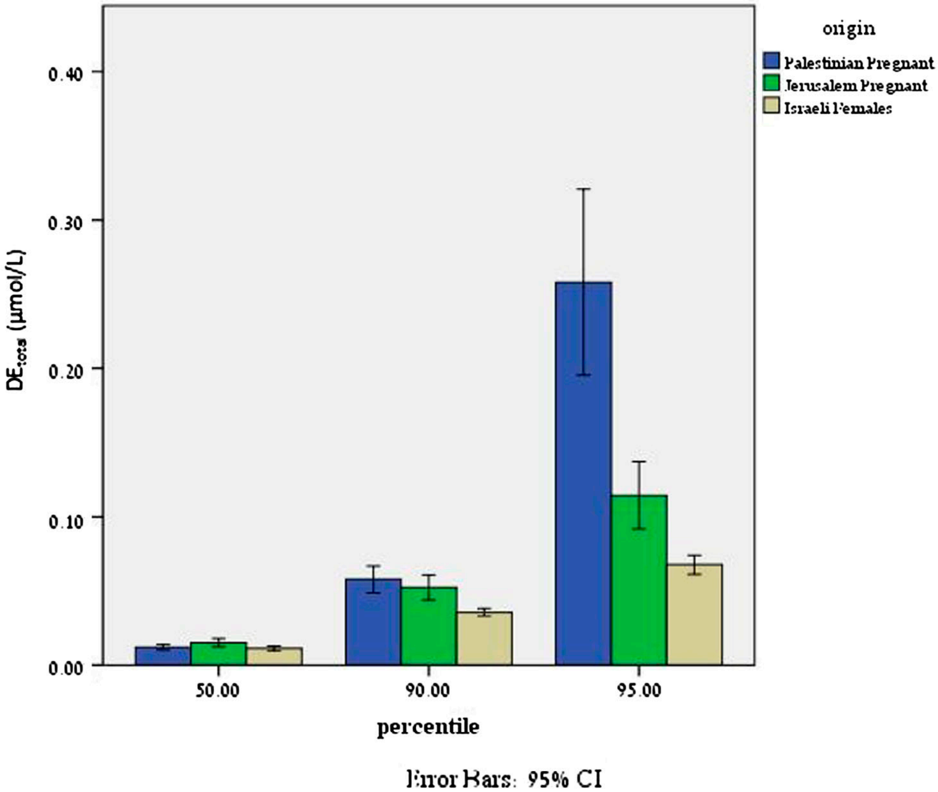

Figure 2. (Color online) Urinary diethyl metabolites (DE_{total}) (μmol/L) in Palestinian pregnant women, Jerusalem pregnant women and women participating in the IBS.

agricultural fields, while 34 % reported that their husband or other family member currently works in agriculture. We emphasize that while urinary OP metabolite levels in Palestinian women were lower than in Israeli women, levels were higher than those in pregnant women in an agricultural community in California (CHAMACOS), a cohort in which maternal OP exposures have been associated with extensive adverse birth outcomes (Bouchard et al. 2011; Eskenazi et al. 2007; Raanan et al. 2015).

One plausible explanation for the lower levels of exposure to OP pesticides in this population is lower intake of fruits and vegetables in the Palestinian population compared to Israelis. In a population-based survey of adults in the West Bank, 80.3 % reported eating less than five servings of fruit and/or vegetables on average per day (WHO 2010). In a study of adolescents in rural areas in Hebron in 2011, more than 90.5 % of study participants reported low consumption of fruits and 88.1 % reported poor consumption of vegetables (Ghrayeb et al. 2014). Results of the Food Consumption Survey of Mothers and Children in the West Bank and the Gaza Strip also indicate low consumption of fruits and vegetables and micronutrient intakes lower than the recommended RDA values (Abdeen & Qasrawi 2010). Possible reasons for low fruit and vegetable consumption include poor health awareness and poor economic status (Ghrayeb et al. 2014). According to a 2009 United Nations World Food Program report,

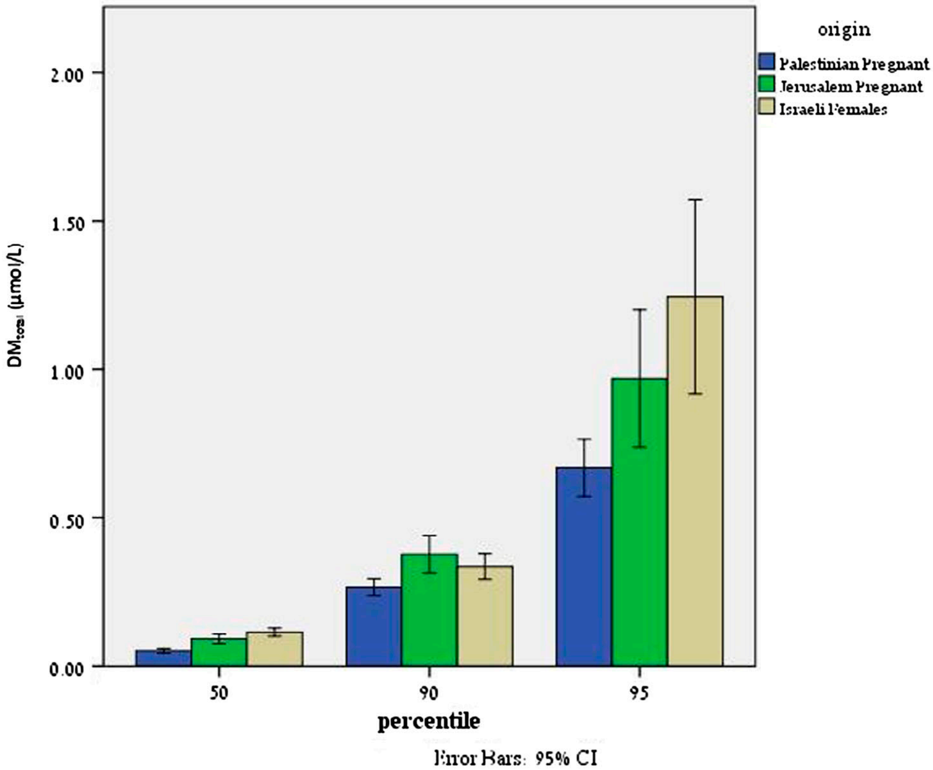

Figure 3. (Color online) Urinary dimethyl metabolites (DM_{total}) (µmol/L) in Palestinian pregnant women, Jerusalem pregnant women and women participating in the IBS.

sales of fruits in the West Bank and Gaza Strip have decreased substantially as a result of high prices (United Nations World Food Programme 2009).

In contrast, fruit and vegetable consumption in Israel is high compared to other OECD countries (OECD 2013). Previous findings on high levels of urinary DAPs in Israeli populations have been attributed to high levels of fruit and vegetable consumption. High fruit intake (above the 75th percentile) is associated with higher urinary DAP levels in the general population in Israel (Berman et al. 2013b). Since we did not collect the same dietary data in all three cohorts we were unable to make comprehensive in-depth dietary comparisons. Our hypothesis that lower exposure levels in the Palestinian population can be explained by dietary patterns is consistent with previous research indicating that diet is the dominant source of exposure to pesticides both in the general population and in rural, occupationally exposed populations (McKone et al. 2007).

It is possible that low consumption of fruits and vegetables in this cohort is associated with low levels of education in this population, as 39 % of the Palestinian women in this study had less than a high school education. Several studies have found that level of education and/ or income is associated with both fruit and vegetable consumption (OECD 2013) and with urinary DAP levels (Ye et al. 2008; Berman et al. 2011; Yolton et al. 2013), indicating that high levels of fruit and vegetable consumption in highly educated individuals results in increased exposure to pesticides. In a recent study on the effects of prenatal OP exposure on neurobehavior in early infancy, women with higher

DAPs were more highly educated and reported more fresh fruit and vegetable consumption (Yolton et al. 2013). It is possible that cultural and dietary habits influencing fruit and vegetable consumption in the populations in our study contribute to lower DAP level in the Palestinian population. In a previous study in the general population in Israel, Arabs, and Druze tended to lower levels of fruit and vegetable intake and lower levels of DAPs compared to Jews, although differences were not significant (Berman et al. 2013b). It is unclear if this difference was related to level of education and/or income, or cultural predictors related to fruit and vegetable consumption.

It is possible that differences in urinary OP metabolite levels are related to differences in pesticide usage and application rates in Palestine and Israel. In 2011, Al-Saeda et al. documented a reduction in pesticides application rates in the agricultural sector in Palestine, possibly related to promotion of integrated pest management by the Ministry of Agriculture (Al-Sa"ed et al. 2011). While we were unable to directly compare application rates in Israel and Palestine, it is noteworthy that Israel is the record-holder among selected OECD countries in the use of pesticides. According to data from the Israel Central Bureau of Statistics, 3.2 tons of active ingredients were used in Israel in 2010 per 10^6 m^2 of agricultural land (Israel Central Bureau of Statistics 2013). In the West Bank, pesticide usage is estimated at 0.22 L/1000 m^2 (Al-Sa"ed et al. 2011). We note that there is extensive trade of fruits and vegetables between Israel and Palestine (Israel State Comptroller 2013), such that agricultural practices in Palestine can impact exposure of Israelis and vice versa.

While median and geometric mean levels were lower in PA women for DM metabolites, and comparable to Israeli populations for DE metabolites, higher maximum DM metabolites and higher 90th percentile, 95th percentile, and maximum concentrations for DE metabolites show that a subset of women in the Palestinian cohort have considerably higher levels of exposure, potentially related to take home exposure and/ or ambient exposure from nearby agricultural fields. Women reporting that they lived near agricultural fields had higher DMP levels than other women. Maximum levels of DMP, DMTP, DETP, and DMDTP were found exclusively in women reporting that they lived near agricultural fields. Similarly, in a cohort of pregnant women from an agricultural community in Salinas Valley, California, overall levels of exposure were similar to a US reference population of pregnant women in the USA, while 95th percentile values were significantly higher in the agricultural community (Castorina et al. 2010).

Our findings regarding higher DMP levels in women reporting living near agricultural fields are consistent with a recent study showing that in women living in agricultural areas in Thailand, urinary DMP concentrations were higher in women who reported that they lived near agricultural areas sprayed with pesticides (Kongtip et al. 2014). In our cohort, current work in agriculture or husband's current work in agriculture was not associated with higher urinary DAP levels, possibly because of the small number of women in these categories ($n = 5$ and 7, respectively). In addition, levels were not higher in 34 women reporting that a family member works in agriculture. Since we did not specifically ask about family members living in the same household as the pregnant women, it is unclear if these family members are a potential source of take-home exposure for the women in this study.

In addition, we note that while total DAPs were lower in the Palestinian cohort compared to Israelis, geometric mean diethyl (DE) metabolites were slightly higher. In Israel, residential pesticides containing chlorpyrifos and diazinon, which metabolize to DE metabolites, were banned in 2007 so residential exposure to OPs in Israel is unlikely. Higher rates of detection and higher levels of DE metabolites may indicate residential sources of exposure to these pesticides in the Palestinian population, such as residential use or storage of these pesticides. Previous data has indicated that chlorpyrifos is present in residential dust samples in Nablus homes (Abdel Raouf Al Faris 2007).

The main strength of the current study is that urine samples from both the Palestinian cohort and the two cohorts for comparison were analyzed by the same analytical procedure and calibration. In addition, one of the cohorts for comparison was a cohort of pregnant women, so the differences we observed are not explained by changes in diet and metabolism that accompany pregnancy.

Our study was limited by differences in questionnaire data collection between the three studies, precluding direct dietary comparisons between the populations. Another major limitation was the fact that only one spot urine sample was collected. In light of high within- person variability in DAP concentrations one urine sample may not accurately reflect OP pesticide exposure (Spaan et al. 2015). In addition, urinary DAP measurements reflect recent exposure to the parent OP pesticides but also to DAPs decomposition products in the environment (Lu et al. 2005). In addition, we did not measure genotype and expression of paraxonase 1 (PON1), a gene involved in metabolism and detoxification of OP pesticides. As there is some evidence that Arabs and Jews may have different PON1 genetic polymorphisms (Frishberg et al. 2000), it is possible that differences in urinary levels of excreted DAPs in the Israeli and Palestinian population are related to genetic differences in PON1. Finally, although we compared pregnant women in this study to non-pregnant women, it is possible that there are physiological changes during pregnancy that effect both the capacity to store OP pesticides and/or their metabolites and pregnancy related changes in hepatic cytochrome P450 metabolism that effect DAP metabolite ratios (Bradman et al. 2005). However, since we compared the Palestinian pregnant women in this study to Jerusalem pregnant women as well, it is unlikely that pregnancy-related changes explain the differences between these populations. Previous studies have shown no major fluctuations in DAP levels throughout pregnancy (Bradman et al. 2005; Kongtip et al. 2014) suggesting that differences in week of gestation between Palestinian and Jerusalem pregnant women do not explain observed differences in metabolite levels.

Our findings on lower GM and median levels of urinary DM metabolites in Palestinian pregnant women should not be interpreted as indicating lower risk of adverse birth outcomes in infants born to these women. Urinary levels in this cohort were higher than those in pregnant women in an agricultural community (CHAMACOS), a cohort in which maternal OP exposures have been associated with extensive adverse birth, developmental, and respiratory outcomes (Bouchard et al. 2011; Eskenazi et al. 2007; Raanan et al. 2015). In addition, high 95th percentile urinary DE levels and significantly higher DMP levels in women living near agricultural fields is of concern. Finally, our hypothesis that lower OP exposures in Palestinian women is related to lower consumption of fruits and vegetable raises concerns for birth and child outcomes in this population, in light of studies showing that maternal fruit and vegetable consumption during pregnancy has been positively linked with fetal growth, as well as protective effects against the development of specific brain tumors such as retinoblastoma (Orjuela et al. 2005; Ramon et al. 2009). In fact, Yolton et al. (2013) found that infants born to women with higher prenatal DE levels had improved attention and reduced lethargy and hypotonia, and that women with higher DAPs had higher levels of education and higher consumption of fruits and vegetables. These findings suggest that the nutritional benefits of high consumption of fruits and vegetables may outweigh the potential harm at the lower range of exposure to OP pesticides.

Conclusions

In conclusion, our findings highlight differences in OP pesticide exposure in populations with close geographical proximity but with differences in culture, diet, lifestyle, and regulatory oversight of pesticides. We are currently evaluating adverse birth outcomes in relation to prenatal exposures to OPs in this population. The results suggest that internal exposures are influenced not only by regional ambient conditions but also by personal dietary habits.

Disclosure statement

No potential conflict of interest was reported by the authors.

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