Effect of phthalates exposure during perinatal period on hormonal profile in Mexican males during their first months of life

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ABSTRACT
Phthalates affect development of male reproductive system acting as an antiandrogenic agents. We sought to explore if perinatal exposure to phthalates could alter male hormone levels in humans during the first months of life. A cohort of 83 pregnant women and their male infants were studied. Five phthalate metabolites were measured in the mother’s urine during the first, second, and third trimesters of pregnancy and during the first, third, and sixth months of life in the infants. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and inhibin B were analyzed. Association between phthalate exposure and hormone variation was assessed using regression models for longitudinal data. Mono-butyl phthalate reduced FSH concentration (β = -0.0012 international units [IU]/L, p < 0.01), mono-ethylhexyl phthalate reduced inhibin B (β = -0.0094 pg/mL, p = 0.02), monoethyl phthalate reduced testosterone (β = -0.0071 ng/L, p = 0.07), mono-ocytl phthalate reduced LH (β = -0.0041 IU/L, p = 0.13). No effects were observed for exposure to mono-methyl phthalate. Our results are consistent with the findings in animal and human studies. Special precaution should be taken when measuring phthalate exposure in susceptible populations such as pregnant women and infants.

1. Introduction
Phthalates are plasticizers which provide flexibility to polyvinyl chloride (PVC) and are widely used worldwide. PVC is used in the manufacturing of blood bags, food packaging, electrical components, pesticides, insect repellents, perfumes, make-up, soaps, detergents, dyes, lacquers, lubricating oils and adhesives. Phthalates also are found in paper, photographic film, toys, bottles and pacifiers. Phthalates as plasticizers are not polymerized within the plastic matrix, instead they are held to the matrix by Van der Waals interactions; thus, they can become dislodged with time and use and released into the environment at which point human exposure can occur [1].

Phthalates affect development of male reproductive system acting as an antiandrogenic agents [2]. Phthalate toxicity is caused by their metabolites. The primary metabolite (monoester) is more toxic than the original compound [3]. The first study of phthalate toxicity in humans was published in 2000 [4]. The following studies showed that phthalates affect semen parameters [5], DNA damage [6], hormonal changes [7], reduction of pregnancy time [8], as well as bronchial asthma [9]. To the date, there are many reports about phthalate effects on human health, such reproductive, metabolic, gynecologic, hormonal, cardiovascular, growth, development and others [10,11].

In infants, sexual hormones levels such as testosterone, gonadotropins and inhibin B are used as biomarkers to test the phthalate reproductive toxicity and their effects in later years. Male hormones are found in all stages of reproductive life of males, from development to adulthood. In humans, the hypothalamic-hypophysis- gonads axis is active since early months of postnatal life, it allows us measure sexual hormone levels and determine if there were phthalate exposure [12,13]. Phthalates acts as endocrine disruptors. Many studies show that exposure...
during pregnancy and infancy may affect the newborn’s health and development [11,14]. Thus, in this study we sought to explore if perinatal exposure to phthalates could alter male hormone levels in humans during the first months of life.

2. Materials and methods

2.1. Population and study design

Longitudinal cohort study of pregnant women and their male newborns was conducted in Toluca metropolitan area, a city in central Mexico located in west of Mexico City. Pregnant women were recruited during their first prenatal visit between the seventh and nineteenth week of pregnancy. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Instituto Nacional de Salud Pública (INSP) under de number CI-056.

Eligibility criteria were pregnant women free of any medication, diabetes or any other chronic diseases. Participants must live in Toluca area for more than 2 years and sign an informed consent. Then a baseline questionnaire was applied by personal interview to address socio demographic information, reproductive, occupational and dietary histories, especially the consumption of dairy products. The same questionnaire was applied in the second and third trimesters of pregnancy to update any information. In each visit a urine sample was obtained to measure phthalates exposure.

After delivery, the infants were appointed during their first, third and sixth month of life to measure their hormone levels and urinary concentration of phthalates. In each visit, infant’s saliva and urine samples were obtained to measure testosterone, gonadotropins, and phthalates, respectively. A questionnaire was applied to elicit information on breast feeding practices and the use of oral infant products.

235 pregnant women met inclusion criteria and they were invited to participate. Fifteen women refused to participate, thus the final cohort was of 220 pregnant women. 8 of whom had spontaneous abortions and 7 were lost to follow-up due to change of address or refusal to continue in the study. Of the total births, 46 % were boys and 54 % girls. Ten of the infants were lost to follow-up due to parental refusal, death, or change of address; in two of these cases no biological samples were obtained.

2.2. Samples collection

To detect their presence across the time it was necessary perform repeated measurements in urine samples from the mothers and newborns. In the mothers, approximately 250 mL of first morning urination from the pregnant women was obtained in preswashed glass flasks that were previously analyzed and found to be free of contamination. The first urine sample was obtained between the seventh and tenth week of pregnancy to evaluate exposure as near as possible to the period at which male sexual differentiation is produced, in addition to identifying possible changes in exposure during the pregnancy. In the infants, 100 mL of urine sample were collected in phthalate-free urine culture bags.

2.3. Phthalates quantification

The primary phthalate metabolites identified were mono-methyl phthalate (MMP); mono-butyl phthalate (MBP); mono-ethyl phthalate (MEP); mono-octyl phthalate (MOP), and mono-ethylhexyl phthalate (MEHP); these corresponded to dimethyl phthalate (DMP), dibutyl phthalate (DBP), diethyl phthalate (DEP), dioctyl phthalate (DOP), and di(2-ethylhexyl) phthalate (DEHP), respectively, which are the most used phthalates as plasticizers in commercial products.

From the mothers, urine sample was collected in each trimester of pregnancy. For the male newborn, urine samples were collected at the first, third and sixth month of life. 50 mL of glucuronidase E solution from E coli were added to urine samples, then pH was adjusted at 6.8 using 0.2 M phosphate buffer. Samples were incubated at 40 °C for twelve hours, at the end of the time pH was adjusted to 2 using concentrated HCl, subsequently 0.1 g of NaCl and 1 mL of HPLC grade methanol were added. Then metabolites extraction was carried out with three portions of dichloromethane. Organic phase was passed through an anhydrous sodium sulfate bed and evaporated at room temperature to final volume of 0.5 mL. The extracted metabolites were derivatize using chloromethyl silane and the volume was adjusted to 0.5 mL with methanol. The extracts were injected into the mass gas chromatograph and quantified with the respective calibration curves. The results were reported as mg/mL adjusted to one g of creatinine [15]. Phthalate measurements were done by triplicate in mothers and male newborns.

2.4. Sexual hormones quantification

Gonadotropins (FSH and LH) were quantified from urine, testosterone in saliva and inhibin B in blood samples. All samples were stored at −20 °C until processing. Testosterone and gonadotropins (FSH and LH) were quantified by immunofluorometry assay (Delfia, Wallac, Finland) with detection limits of 0.03 nmol/L and 0.05 U/L, respectively. Inhibin B was quantified by enzyme-linked immunosorinet assay (ELISA) (Inhibin-B Assay, Bio-innovation, Ltd., Oxford, UK), with detection limits of 18 pg/mL. Immunofluorometry and ELISA assays were performed using the manufacturer’s recommendations. FSH, LH, and testosterone assays were made by triplicate, while inhibin B assay was performed only once.

2.5. Statistical analysis

Statistical analysis included the phthalates and hormone concentrations at each point of their measurement expressed by geometric means and 95 % confidence intervals since hormone concentrations did not follow normal distribution. To evaluate associations, hormone values were transformed to logarithmic scales.

The co-variables associated with hormone levels were: (1) age, (2) levels of other hormones from the hypothalamic-hypophysis-gonad axis, and (3) creatinine present in the urine. To test the association between hormones and phthalates we used Generalized Estimating Equations (GEE) models to longitudinal data [16]. To correct for urine dilution, creatinine was included in the multivariate model as an independent variable following the recommendations by Barr 2005 [17]. All data were analyzed using the Staeta Statistical Software (StataCorp 2003) [18].

3. Results

A total of 83 children were included in the study; 80 % were born vaginally, while 20 % were born via cesarean section. 38 weeks was the average of gestation time, with a standard deviation (SD) of 1.8. The American Pediatric Gross Assessment Record (APGAR) at birth was 7–10 in 95 % of the children, while < 5% obtained an APGAR score < 7. The average birth weight was 3090 g (SD, 487 g) and the mean maternal age was 24 years old (SD, 4.7 years).

Table 1 shows the quantity of the 5 primary phthalate metabolites during the pregnancy and postnatal periods. In the pregnancy, MEHP levels were the highest during the first and third trimester trimesters; during second trimester MEP had the highest level. While MOP showed the lowest levels at the first trimester and MMP and MBP for the second and finally MPP for the third trimester. There is not any special or obvious reason that explains this result. During the first months of life, MBP levels were the highest, followed by MEHP and MEP; however, at 6 months of age MEHP concentrations increased notably compared to the MMP levels. Finally, at 27th week MBP showed the highest value being 3.5 times higher than MEP, MEHP and MOP and 20 times higher than
Table 1
Geometric mean levels of five phthalate metabolites measured in Mexican pregnant women and their male infants by the exposure period.

| Exposure period       | Weeka | (N)   | MMP** (μg/mL) | MEP** (μg/mL) | MBP** (μg/mL) | MEHP** (μg/mL) | MOP** (μg/mL) |
|-----------------------|-------|-------|---------------|---------------|---------------|---------------|---------------|
| **Prenatal (Pregnant women)** | 11    | (83)  | 0.335         | 0.462         | 0.461         | 0.552         | 0.328         |
|                       |       |       | (0.222, 0.504)| (0.292, 0.730)| (0.275, 0.771)| (0.382, 0.796)| (0.209, 0.515)|
|                       | 22    | (78)  | 0.194         | 0.608         | 0.194         | 0.544         | 0.501         |
|                       |       |       | (0.159, 0.236)| (0.401, 0.922)| (0.159, 0.236)| (0.368, 0.806)| (0.299,0.838)|
|                       | 35    | (78)  | 0.190         | 0.650         | 0.370         | 0.678         | 0.232         |
|                       |       |       | (0.154, 0.237)| (0.391, 1.079)| (0.222, 0.615)| (0.409, 1.124)| (0.163, 0.330)|
| **Post-natal (Infants)** | 4     | (77)  | 0.211         | 0.439         | 0.766         | 0.692         | 0.264         |
|                       |       |       | (0.164, 0.272)| (0.304, 0.633)| (0.431, 1.333)| (0.459, 1.044)| (0.187, 0.372)|
|                       | 14    | (79)  | 0.216         | 0.790         | 2.136         | 2.522         | 0.173         |
|                       |       |       | (0.156, 0.299)| (0.480, 1.330)| (1.040, 4.380)| (1.598, 4.528)| (0.140, 0.213)|
|                       | 27    | (79)  | 0.428         | 2.303         | 7.845         | 2.056         | 0.219         |
|                       |       |       | (0.250, 0.734)| (1.223, 4.301)| (3.402, 18.066)| (1.061, 3.983)| (0.151, 0.317)|

MOP = Mono-Octyl Phthalate.
Nono-ethylhexyl phthalate (MEHP) levels being higher during the three pregnancy trimesters, followed by mono-ethyl phthalate (MEP) and mono-butyl phthalate (MBP).

During the first months of life, MEHP levels were higher, followed by MBP; however, at 6 months of age MBP concentrations increased notably compared to the MEHP levels.

MMP.

Table 2 shows hormone at 4th, 14th and 27th week. Testosterone and LH levels were higher at 1 month of age (4th week) than the 14th and 27th weeks. FSH increased between the second and third measurements. The mean inhibin B level obtained during the 14th week was 522.1 pg/mL.

Table 3 includes the association between phthalate and hormone levels. In general, all hormones reduced their levels, although not all coefficients were statistically significant. FSH levels were reduced by MBP (β = −0.0012, p = 0.001), inhibin B by the MEHP (β = −0.0094, p = 0.02), testosterone by MEP (β = −0.0071, p = 0.07), and LH by MOP (β = −0.0041, p = 0.13). In these cases, the coefficient was negative and the p-values were statistically significant for the associations of MBP and FSH, and MEHP and inhibin B. MMP reduces FSH levels. MEHP reduces inhibin B levels. No hormonal changes were observed with MMP.

Table 4 shows a comparison of urinary phthalates metabolite median levels in the NHANES and among pregnant women from New York City (NYC), Denmark, Canada, several United States (US) cities*, Boston, Mexico and Greece.

4. Discussion

There is a paucity of research on phthalate exposure in human populations and even fewer studies have evaluated the mother-child bi-

Table 2
Mean testosterone, FSH, LH and Inhibin β levels in Mexican infants during the first six months of life (in weeks).

| Hormones                  | Week | (N) | Mean ± std test for deviation trend (SD) | P-value |
|---------------------------|------|-----|-----------------------------------------|---------|
| **Testosterone (nmol/l)** | 4    | (78)| 1.81 (3.56)                             | <0.01   |
|                           | 14   | (79)| 0.76 (1.50)                             |         |
|                           | 27   | (75)| 0.38 (0.61)                             |         |
| **FSH (u/L)**             | 4    | (75)| 1.43 (1.93)                             | 0.23    |
|                           | 14   | (80)| 1.19 (1.50)                             |         |
|                           | 27   | (76)| 1.59 (2.34)                             |         |
| **LH (u/L)**              | 4    | (75)| 1.59 (2.32)                             | 0.03    |
|                           | 14   | (80)| 1.15 (1.14)                             |         |
|                           | 27   | (76)| 0.69 (0.89)                             | <0.01   |
| **Inhibin β (pg/mL)**     | 14   | (68)| 522.1 (342.8)                           |         |

* FSH = Follicle-stimulating hormone, LH = Luteinizing hormone.

Phthalate metabolites (μg/mL)
Geometric mean (95% CI)

Table 3
Regression coefficients for the association between testosterone, FSH*, LH*, Inhibin β and phthalate metabolite average levels adjusted by exposure period** (weeks), creatinine and hormonal levels.

| Phthalate metabolites | Testosterone log | FSH log | LH log | Inhibin β log |
|-----------------------|-----------------|---------|--------|---------------|
| **MBP** (95 % CI)     | -0.0012         | 0.0047  | 0.0002 | 0.0012        |
| P-value               | 0.078           | 0.001   | 0.18   | 0.56          |
| **MEHP** (95 % CI)    | -0.0070         | 0.0067  | 0.0061 | 0.0094        |
| P-value               | 0.58            | 0.55    | 0.55   |               |
| **MEP** (95 % CI)     | -0.0071         | 0.0022  | -0.0033| 0.0034        |
| P-value               | 0.07            | 0.50    | 0.28   | 0.31          |
| **MOP** (95 % CI)     | -0.0033         | 0.0037  | -0.004 | 0.0043        |
| P-value               | 0.33            | 0.21    | 0.13   | 0.09          |
| **MMP** (95 % CI)     | -0.0048         | -0.0040 | 0.0039 | -0.0010       |
| P-value               | 0.18            | 0.21    | 0.18   | 0.67          |

MMP = Mono-Methyl phthalate.
Cut off value of p was ≤ 0.05.

** Pre and post-natal periods.
*** MMP = Mono-Butyl phthalate, MEHP = Mono-Ethylhexyl phthalate, MEP = Mono-Ethyl phthalate, MOP = Mono-Octyl phthalate.

nomine in Latin America. Our study found lower phthalate concentration levels than those reported by Adibi 2003 [19] in four populations of pregnant women in New York and in Krakow, Poland; in China [20,21] and in South Korea [22]. These studies showed variations in phthalates concentrations in pregnancy woman. Such differences may be due to feeding habits given that diet is the principal source of phthalate
Phthalates are common in household products such as diapers, toys, and packaging materials. They are also present in food, water, and air. Studies have shown that exposure to phthalates can affect various physiological functions, including endocrine disruption, neurodevelopment, and respiratory health. The effects of phthalate exposure have been investigated in both animal models and human populations, with varying results.

### Table 4

| Phthalate Metabolites | NHANES 1988-1994 | NHANES 1999-2000 | NYC Adibi et al. (2003) | Denmark Toft et al. (2012) | NY Kroobly et al. (2014) | Canada Arbuckle et al. (2014) | Several US cities** Serrano et al. (2014) | Boston Braun et al. (2014) | Canada Fisher et al. (2015) | Mexico Bustamante-Montes et al. (2013) | Crete, Greece Katsikantami et al. (2020) |
|-----------------------|------------------|------------------|------------------------|--------------------------|------------------------|----------------------------|--------------------------------|--------------------------|--------------------------------|--------------------------------|----------------------------------|
| MBP                   | 41.0             | 25.0             | 42.6                   | 225.1                    | 13.61                  | –                          | –                              | 77.8                     | 23                             | 11.23                           | 28.1                             |
| MEBP                  | 2.7              | 3.2              | 4.60                   | 16.2                     | 3.65                   | 2.24                       | 2.54                          | –                         | 2.26                           | 3.48                             | 6.1                              |
| MEP                   | 305.0            | 164              | 230.6                  | 405.8                    | 81.01                  | 32.02                      | 35.63                         | 309.5                    | 42.5                           | 34.88                           | –                                |
| MBzP                  | 21.2             | 17.0             | 121.2                  | 20.3                     | 6.59                   | 5.20                       | 4.28                          | –                         | 10.7                           | –                                | 46.7                             |

* NHANES = National Health and Nutrition Examination Survey, ** Metabolites = Mono-Ethyl Phthalate, MEBP = Mono-Ethyl-Hexyl Phthalate, MEP = Mono-Propyl Phthalate, MBzP = Mono-Benzyl Phthalate.

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