Prenatal Exposure to Phthalates, a Potential Cause of Adverse Fetal Outcomes: A Systematic Review

John M. Nightingale

Physician Assistant

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Abstract
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Methods: A systematic review of studies written between 2000 and 2010, using published literature in the English-language, was conducted using MEDLINE, Evidence-Based Medicine Reviews Multifile, and Web of Science using keywords phthalate, phthalates, prenatal, anogenital distance, AGD, birth, low birth weight and birth outcomes. Articles that examined the birth outcomes of birth weight, birth length, head circumference and gestational age after in utero exposure to phthalates were selected. Four studies were analyzed for result outcomes.

Results: Three of the four studies have demonstrated that in utero exposure to environmental phthalates is associated with either newborn birth weight, birth length, head circumference or gestational age. The forth study reported no significant relationships between prenatal exposure to phthalates and any of the birth outcomes.

Conclusion: The findings deduced in this study using the GRADE process, suggest that, at the current level of exposure, phthalates may have subtle affects on the fetus in relation to certain birth outcomes. However, the evidence is of low quality and further investigation is needed to truly report that these findings are not due to other limitations such as other environmental chemicals not evaluated or confounding factors such as self-reported values.

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Prenatal Exposure to Phthalates, a Potential Cause of Adverse Fetal Outcomes: A Systematic Review

John M. Nightingale

A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

Pacific University School of Physician Assistant Studies

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INTRODUCTION

Background

Phthalates are chemical additives that act as fixatives and solvents, and are widely used in consumer products to carry fragrances and soften plastics. They are found in a wide range of vinyl plastic products from toys to medical equipment. However, they are also found in personal care products and foods, including infant formula and baby food (Stillerman, Mattison, Giudice, & Woodruff, 2008). Phthalates have been found to be ubiquitous in our daily environments (Zhang et al., 2009). They are volatile in nature and leach out of products, at measurable rates, into the surrounding environment. Varying levels of exposure are present in everyone on a daily basis dependent on fluctuating degrees of exposure and the body’s ability to metabolize these chemicals, which is relatively quickly, from a few hours or within days (Huang, Kuo, Chou, Lin, & Lee, 2009; Zhang et al., 2009).

To date, phthalates have been studied for a verity of outcomes on animals and humans, and there has been developing concern that phthalates pose harm to humans in a number of ways. One particular concern is the potential harm to the fetus. Increased understanding shows that there are sensitive windows of development to the individual fetal biologic systems, such as – cardiovascular, respiratory, endocrine and even general growth (Stillerman et al., 2008), that, if even exposed to subtle amounts of chemicals, may alter the function and morphology of that fetus (Suzuki et al., 2010). One study mentioned, “Changes in birth weight or early body weight in rodents after prenatal exposure to various phthalates have been reported (Sharpe et al. 1995; Tanaka 2002, 2003, 2005), but reports of no effects also exist (Arcadi et al. 1998; Hoshino et al. 2005)”
(Wolff et al., 2008, p. 1092). Of concern here are the effects phthalates may have on birth outcomes, for example as with “birth weight and length of gestation, [as these] are important predictors of neonate and infant health” (Stillerman et al., 2008, p. 632). “Low birth weight (LBW) is one of the leading causes of mortality in children under age 5 years and is associated with increased risk of cardiovascular and metabolic disease in adulthood” (Zhang et al., 2009, p. 500). In addition, low birth weight infants “… also experience significantly higher rates of morbidity during the perinatal period than term and normal birth weight infants” (Stillerman et al., 2008, p. 632). Studies have thus been looking at how these chemicals affect humans to answer the questions that remain concerning the overall effect that phthalates pose on these and other human biologic systems before and after birth.

Purpose of the Study

The purpose of this paper is to conduct a systematic review of the literature to determine the teratogenic effects of in utero fetal exposure to phthalates and birth outcomes broken down into four groups – birth weight, birth length, head circumference, and gestational age. This was accomplished using the “GRADE” stepwise approach to evaluating studies and their outcomes.

METHOD

An extensive literature search was performed using MEDLINE, Evidence-Based Medicine Reviews Multifile, and Web of Science. All databases were accessed through the Pacific University Library System. The key words searched included phthalate,
phthalates, prenatal, anogenital distance, AGD, birth, low birth weight and birth outcomes, individually and in combination. The search was limited to human subjects, the English language, and studies completed between 2000 and 2010. Once combined, this resulted in nine studies to review from Medline, 10 from Evidence-Based Medicine Reviews Multifile, and 20 from Web of Science. Further review of these articles was needed to verify study purposes and outcomes, and to extract duplicated references, animal studies, or letters to the editor. Four articles were acquired and set for review.

Exclusion criteria included articles with animals and articles that focused more on potential behavioral affects of phthalates on children. Letters to the editor, descriptive studies and articles without full text accessibility were excluded. Only cohort and case-control studies were identified, as performing randomized trials of this nature would be unethical.

Between 2008 and 2010 four studies were published that met the criteria for evaluating the risk to the fetus of exposure to phthalates. The types of phthalates evaluated and their metabolites were reported in all studies. The newborns birth weight, birth length, and gestational age were reported by all studies, but head circumference was only measured and reported by two of the studies. Maternal urine samples were used by the three cohort studies, to evaluate phthalate exposure levels, where as the case-control study used maternal blood, umbilical vein blood and neonate meconium samples for phthalate or phthalate metabolite levels. Amniocenteses were performed on all subjects prior to giving birth only in one cohort study. Maternal demographics, anthropometrics, number of pregnancies and social-economic factors were taken and considered by all studies, but only three provided the data in their reports. Newborns were otherwise heal-
thy in all studies. The sample size ultimately ranged between 65 mother-infant pairs to 352 after adjusting for incomplete data on participants and those lost to follow up for various reasons. Studies were either cohorts (3) or case-controls (1).

RESULTS

Of the four studies included in this systematic review, three were cohort studies and one was a case control study that studied the birth outcomes of newborns that were exposed in utero to phthalates.

The Huang et al. (2009) study, is a cohort study that took place during 2005-2006, in Taiwan. They started with 83 participants who had planned to undergo amniocentesis due to indications of “advanced age” or “abnormal maternal serum screening (alpha fetal protein and β-hCG)”, and complete information on 65 of the participants was reported. No explanation was given for the 18 lost at this point. All participants and their fetuses were diagnosed healthy after chromosome evaluation of the amniotic fluid. Due to significant differences between the males and females in birth weight, length and gestational age, they grouped the newborns according to gender for statistical analysis.

The analysis of the amniotic fluid in Huang et al. (2009) found that the fetuses were overall exposed to di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP) as the metabolite detectable rates found in the fluid were 100% for monobutyl phthalate (MBP) and >90% for mono-2-ethylhexyl phthalate (MEHP). Trace amounts of other phthalates were found and not reported. One sample failed during this analysis.

The maternal urinary analysis measured five metabolites MBP, MEHP, monoethyl phthalate (MEP), mono methyl phthalate (MMP), and mono benzyl phthalate
(MBzP) with the highest concentrations being for the first three at 100%, 98%, 96%, respectively. They report that fetal exposure during “early pregnancy” was to DBP, DEHP and DEP. Compared together there was “…a significant positive correlation only between urinary MBP and amniotic MBP in all newborns ($R^2 = 0.156, p = 0.002$)” (Huang et al., 2009, p.16).

Of the male newborns in the study, there were no significant differences found in exposures to phthalates in any category. For the female newborns, those categorized to the high-level MBP-AF (monobutyl phthalate-amniotic fluid) had significantly higher ($p = 0.031$) birth weights and lengths as compared to the low-level MBP-AF group ($p = 0.018$). In this study, high and low-level MBP-AF refers to higher or lower concentrations of phthalates in amniotic fluid. Of these same groups, they go on to discuss the differences found in anogenital distances (AGD’s) that were found to be shorter in the high-level MBP-AF group, with the larger birth weights and lengths, as compared to the low-level MBP-AF group (13.9mm vs 17.6mm, $p = 0.024$). Then, to adjust for differences in weight and length an anogenital index (AGI) was calculated for each. Of the two values obtained, the smaller value was linked to the high-level MBP-AF group. The values being 4.5mm/kg to 6.2mm/kg, $p < 0.01$ for the AGI-Ws and 2.8 to 3.7 for AGI-L, $p < 0.01$. This significance was also found in the MEHP-AF groups, high and low-level values of 4.7mm/kg to 6.0mm/kg in the AGI-Ws, $p < 0.05$ and 2.8 to 3.6 for AGI-L, $p < 0.05$. The authors concluded that they found a significantly negative correlation between amniotic fluid MBP and AGD and AGI-W.

The second study reviewed was conducted by Suzuki et al. (2010), who specifically looked for nine different phthalate ester metabolites in the urine of 149
healthy pregnant Japanese women living in Tokyo, Japan during 2005-2008, and evaluated their newborns’ birth outcomes for variations. Of the nine metabolites looked at, MMP, MEP, mono-n-butyl phthalate (MnBP), MBzP, MEHP, mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxyhexyl phthalate (MEOHP), mono-iso-nonyl phthalate (MINP) and mono-n-octyl phthalate (MnOP) they found no statistically significant correlation between the metabolites and birth outcomes for the individual phthalate ester metabolites or when they were lumped into high and low-molecular weight phthalate (MWP) sum groups.

The third study reviewed, Wolff et al. (2008), was an American cohort study that began with 382 young, healthy, “largely nonwhite,” mother-infant pairs, in New York City from 1998 to 2002. The final sample size was 352 – 190 Hispanic, 107 Black, 80 White and 5 Other. Their research pertained to third trimester phthalate exposures. Urine levels of phthalate biomarkers were found on ten different metabolites those being mono-2-ethyl-5-carboxypentyl phthalate (MECPP), MEHHP, MEOHP, MEHP, MBzP, mono-3-carboxypropyl phthalate (MCPP), monoisobutyl (MiBP), MBP, MEP and MMP. From these ten phthalate metabolites, three groups were formed, to analyze the micromolar sums (µmol/L), two were according to the molecular weight of the individual metabolites – low-MWP (MiBP, MBP, MEP, MMP) and high-MWP (MECPP, MEHHP, MEOHP, MEHP, MBzP, MCPP), the other group – DEHP-MWP (MECPP, MEHHP, MEOHP, MEHP) because these four metabolite all originate from DEHP. They found no significant association of the latter two groups for any birth outcome, whereas, the “low-MWP metabolites were positively associated with head circumference (β = 0.13 cm; 95% CI, 0.01-0.24cm) and gestational age (β = 0.14 week; 95% CI, 0.01-0.27week).” The
tertiles of the low-MWP metabolites on head circumference were not significantly associated with phthalate exposure, (no data provided). Whereas, the second and third tertiles on gestational age for “low-MWP metabolites predicted 0.4 week longer gestation compared with the first tertile (adjusted predicted means: third tertile, 39.6 weeks; 95% CI, 39.1-40.1 weeks; second tertile, 39.7 weeks; 95% CI, 39.2-40.2 weeks; first tertile, 39.2 weeks; 95% CI, 38.7-39.6 weeks)” (Wolff et al., 2008, p. 1095).

Lastly, Zhang et al. (2009), is a case-control study that evaluated 201 Chinese mother-infant pairs living in Shanghai, China during 2005-2006. Eighty-eight low birth weight (LBW < 2,500g) term (>37weeks) newborn cases and 113 normal birth weight term newborn controls (birth weight ≥ 2,500g) were compared. They used maternal and cord blood along with newborn meconium samples to evaluate types and amounts of phthalate exposure to DEP, DBP, and DEHP and two monoester metabolites derived from these three, MBP and MEHP.

Initially, Zhang et al. (2009) reported that the LBW cases had higher levels of phthalates and monoesters as compared to the controls. The significant odds ratios (OR) and confidence intervals (CI) were found and maternal blood DBP results were 2.2 (1.4 – 3.2) for the control group, and 2.9 (2.5 – 3.4) for LBW cases with p = .02; for maternal blood MEHP 1.4 (1.2 – 2.1) for the control, and 2.9 (1.8 – 3.5) for LBW cases with p = .000. In cord blood the OR and CI were reported for DBP as 1.8 (1.2 – 2.7) for control, and 2.7 (2.2 – 3.0) for LBW cases p = .002, and for cord blood MEHP values of 1.1 (0.9 – 1.7) for control and 2.5 (1.6 – 3.4) for LBW cases with p = .000. In neonate meconium the values for MBP were 1.7 (1.2 – 2.4) for the control group, and 2.2 (1.6 – 3.6) in the
LBW cases, with \( p = .003 \), and neonate meconium MEHP values were 2.9 (1.8 – 4.4) for the control, and 5.5 (3.4 – 9.3) for the LBW cases, with \( p = .000 \), (Zhang et al., 2009).

Secondly, using Spearman correlations, they found that LBW was significantly associated with in utero exposure to DBP in cord blood, correlation coefficient of -0.23 with \( p = 0.01 \), and in meconium -0.56 with \( p = 0.000 \). Shorter birth length was associated with cord blood DEHP exposure with values of -0.22 with \( p = 0.05 \), and meconium MEHP values of -0.47 with \( p = 0.000 \).

Lastly, dose-response relationships were found, and an increased risk of LBW was linked to the highest quartiles of DBP and DEHP concentrations. They reported the OR and CI’s of 3.54 (1.54-6.15) \( p = 0.008 \) and 2.05 (1.17-3.70) \( p = 0.05 \), respectively. Again dose-response relationships were found between the MEHP in its highest quartile of meconium level and LBW, 3.23 (1.31 – 5.94) \( p = 0.04 \). “For DBP, a dose-response relationship was found between LBW and both DBP level in cord blood and MBP level in meconium” (Zhang et al., 2009, p. 502). As for DEP and DEHP, differences were not observed between LBW infants and controls.

DISCUSSION

Phthalates are commonly used chemicals in our society, and thus exposure to these pollutants occurs nearly every day. Concerns for potential human structural alterations (birth defects) related to in utero exposure to phthalates have developed from many animal studies that have found issues affecting development, thus the question here is how do these chemicals affect humans in this critical time of development in relation to
birth weight, birth length, head circumference and gestational age. The four studies reviewed were evaluated using GRADE to rate the quality of evidence.

The first graded outcome was birth weight, as all studies reported on this finding. Interestingly enough, the reported GRADE findings were mixed between association and no association of phthalates and birth weight. Firstly, this group's study quality was decreased due to negligence in reporting 18 subjects information and why they were lost to follow-up, as well as not reporting the maternal demographics (i.e. age, number of pregnancies, anthropometrics, social habits and socio-economic factors) by (Huang et al., 2009). To go along with study quality, only Zhang et al. (2009) reported any blinding of any kind. Thus, this lack of reporting decreased the grade in study quality for BW outcomes.

Due to variability in the reported results for BW outcomes, the area of consistency was dock a point. Of the 3 phthalates and the 13 phthalate metabolites measured between all studies, only one particular phthalate was related in both studies that found associations to BW, di-n-butyl phthalate (DBP) and its metabolite monobutyl phthalate (MBP). Of these findings, that associated phthalates with BW, there was opposite affects reported, one being for an increased birth weight associated with MBP only in female newborns and the other found an association between low birth weight (LBW) and DBP. These were Huang et al. (2009) and Zhang et al. (2009), respectively. The other two cohorts, Suzuki et al. (2010) and Wolff et al. (2008), both reported no association between BW and any of the nine or ten, respective, phthalate ester metabolites measured. One last concern for study quality lies in the fact that the case-control by Zhang et al. (2009) was the only study to not use urine samples to evaluate phthalates, instead they
used maternal blood, umbilical vein blood and neonate meconium. This is not to say they are wrong by doing so, but in matters of being evaluated on the same level as the other studies this had to be taken into account for determining the grade. Down grading the studies for the above stated lack of consistencies was deemed appropriate.

Precision was questioned for BW, as all studies reported their levels of significance in various statistical forms, and confidence intervals (CI) were not given in all studies, making it difficult to verify their precision. Size of the study populations were also regarded for precision and found that the smallest cohort, Huang et al. (2009) and the case-control, Zhang et al. (2009), had the most significant findings in regards to BW. The two largest cohorts, Suzuki et al. (2010) and Wolff et al. (2008), found no association to BW.

The directness and publication bias were left the same, as all studies appear to not impede on these qualities.

However, Zhang et al. (2009) reported a dose-response in their case-control between levels of DBP, MBP, MEHP and LBW. This was noted along with the well discussed confounders and limitations and points were added to each category.

The evidence for BW started and ended with a Low rating after all was taken into account.

The second graded outcome was birth length (BL). This category comprised all four studies being reviewed as well, and here the findings were found to be mixed between association and no association of phthalates and BL.
In the area of study quality for BL, due to factors of unreported reasons for loss to follow-up, lack of maternal demographic data reporting and lack of blinding this category was marked down for the lack of detail, as mentioned above in more detail under BW.

As for consistency for BL outcomes, a deduction was made for the variations in the split associations between increased and decreased BL, and two no associations. MBP was reported to cause an increased BL in female newborns only and DEHP actually caused decreases in BL as per Huang et al. (2009) and Zhang et al. (2009) respectively. Wolff et al. (2008) actually showed one individual value for monobenzyl phthalate (MBzP) as being significant to BL on its own, but when placed in its high-molecular weight phthalate (high-MWP) group to figure the sum it lost significance and so along with Suzuki et al. (2010) they declared no association between phthalate metabolites and BL. All other categories for the GRADE table, under BL, were unchanged. These weaknesses brought the starting grade for BL down from Low to Very Low.

Head circumference (HC) was the third graded outcome and only involved two cohort studies Suzuki et al. (2010) and Wolff et al. (2008). All categories to decrease the grade were unchanged as these studies showed no need to lower the grade although, variation in consistency was questioned as Wolff et al. (2008) noted an association in the low-molecular weight phthalate (low-MWP) group and HC where Suzuki et al. (2010) found no association. However, in Wolff et al. (2008), their tertile for the low-MWP group found no significance. As for increasing the HC grade, sufficient delineation of the possible confounders associated with HC ultimately marked up this groups starting grade from Low to Moderate evidence.
The fourth and final graded outcome, gestational age (GA), involved all three cohorts, of which only one, Wolff et al., found an association between GA and phthalates. The study quality was marked down for the lack of reporting of the loss to follow-up reasons and maternal demographic information as mentioned before in Huang et al. (2009). In addition, since Wolff et al. (2008) found a small increase in GA in relation to the low-MWP group, the consistency varied between association and no association, and thus gave more strength in decreasing this category. However, the discussion on GA confounders was very in depth and was explained well especially by Wolff et al. (2008) who found the association. They explain that these findings may “…reflect unresolved confounding…” (Wolff et al., 2008, p. 1095) due to correlations found between low-MWP and BMI, BMI and GA, and between low-MWP and creatinine, and concluded that maternal anthropometrics may affect the low-MWP exposure level, the creatinine measurement and the outcome measurement. And due to rough self-reported anthropometrics confounding was possible (Wolff et al., 2008). Given these factors, the GA group was given an increase in the area of confounders. All other categories were unchanged to the GRADE chart, leaving the GA group with a Very Low evidence rating.

Pooling the evidence, on the GRADE chart, from each grouping, the “Low” for birth weight, the “Very low” for birth length, the “Moderate” for head circumference and the “Very Low” for Gestational Age, altogether, give the overall grade of evidence as “Low”. This “Low” rating, suggest that future research will very likely provide better confidence in the estimate of association between phthalates and birth outcomes.
As these findings of decreased birth weight, length, head circumference or gestational age may not initially seem to be a big concern, clinically speaking, studies have found that factors such as “low birth weight infants experience longer hospital stays at birth and a greatly increased risk of respiratory distress syndrome. Intrauterine growth restriction has been identified as a significant risk factor for chronic hypertension, heart disease, lung disease, and type 2 diabetes later in life, creating the need to understand the impact of adverse pregnancy outcome across the life course” (Stillerman et al., 2008, p. 632). They go on to strongly mention that “adverse birth outcomes are a financial and emotional burden on families both in the short and long term. Average hospital charges for premature births in 2003, for example, have been estimated to be $18.1 billion, about half the total infant hospital charges for all US births” (Stillerman et al., 2008, p. 632). For this purpose, phthalates should continue to be studied and evaluated to assure quality of life from beginning to end.

For future studies, in relation to phthalates and birth outcomes, other confounders and limitations were mentioned by these studies, a few of which that were not previously mentioned above are mentionable here. Huang et al. (2009) mentioned that only one urinary and amniotic phthalate metabolite (MBP) was found to have a modest correlation, where the other metabolites measured showed no significance. They concluded that this may possibly be that the non-significant phthalate, DEP, in this case, has a short, 4-hour half-life in humans, which lead to decreased levels available to cross from the mother into the placenta. Another limitation noted in the studies was the inability to completely assess the sources and amounts of exposure for each individual phthalate to each pregnant woman, not to mention the list of other known chemicals that can cause changes
to birth outcomes for which exposures were not accounted for in these studies (Huang et al., 2009; Suzuki et al., 2010; Wolff et al., 2008; Zhang et al., 2009). And though the majority of these studies factored in smoking, side stream smoke at home or in the work environment was not taken into account but it is definitely a factor that could affect birth weight (Zhang et al., 2009). Though there are many factors to take into account, and though the evidence presented here was Low for the current level of exposures and there outcomes, clinically there is still a need to verify that in utero exposures to phthalates are not causing problems to the fetus, and, that may, cause problem later on in life.
REFERENCES


### Grade Table for Phthalates and Birth Outcomes

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<thead>
<tr>
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<th>Findings</th>
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<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>GRADE of Evidence for Outcome</th>
<th>Overall GRADE of Evidence Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3 Cohorts and 1 Case-control</td>
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<td>Low</td>
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<tr>
<td>Birth Length</td>
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<td>Mixed – Association and no Association</td>
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<tr>
<td>Gestation Age</td>
<td>3 Cohorts</td>
<td>Mixed – Association and no Association</td>
<td>Low</td>
<td>-1</td>
<td>0</td>
<td>Very Low</td>
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Table of Phthalates and Phthalate metabolites measured in each study

<table>
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<th>Huang et al. - Taiwan</th>
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<th>Suzuki et al. - Japan</th>
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<td>MBP</td>
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<td>MBzP</td>
<td>MBP</td>
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