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NEONATAL MECONIUM AS A BIOMARKER FOR PRENATAL EXPOSURE TO ETHINYL ESTRADIOL, SULFAMETHOXAZOLE, AND IBUPROFEN

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ABSTRACT

Prenatal exposure to pharmaceutical compounds and endocrine-active substances represents an important public health concern due to their potential effects on fetal development. Neonatal meconium has emerged as a valuable biological matrix for assessing in utero exposure, as it accumulates xenobiotics during the second and third trimesters of pregnancy. This cross-sectional study aimed to evaluate neonatal meconium as a biomarker for prenatal exposure to ethinyl estradiol, sulfamethoxazole, and ibuprofen among newborns delivered in selected hospitals in Lattakia and Damascus, Syria. A total of 123 meconium samples were collected from term neonates within the first 24 hours after birth. Maternal and neonatal data were obtained from medical records. Mothers younger than 18 years or diagnosed with pregnancy-related conditions such as gestational diabetes or hypertension were excluded. Neonates with congenital anomalies, pregnancy complications, or preterm birth (<37 weeks of gestation) were also excluded. Meconium samples (5–10 g) were collected in sterile containers, stored at −20 °C, and subjected to wet digestion using nitric acid (HNO_3) assisted by microwave digestion for compound extraction. Quantitative analysis was performed using high-performance liquid chromatography (HPLC) with an Agilent 1100 system, following standard analytical specifications. The findings of this study support the applicability of neonatal meconium as a reliable non-invasive matrix for assessing prenatal exposure to selected pharmaceuticals. This approach may contribute to improved monitoring of fetal exposure to commonly used medications and endocrine-active compounds during pregnancy.

KEYWORDS: Meconium analysis; prenatal drug exposure; ethinyl estradiol; sulfamethoxazole; ibuprofen; HPLC.

INTRODUCTION

Exposure to pharmaceutical compounds during pregnancy has become an issue of growing concern, particularly as many commonly used medications are capable of crossing the placental barrier and reaching the developing fetus. While certain drugs are considered relatively safe when clinically indicated, unintentional or repeated exposure during pregnancy may still influence fetal growth and development, especially during critical windows of gestation. For this reason, there is increasing interest in identifying reliable biomarkers that can reflect cumulative prenatal exposure to selected pharmaceuticals.

Neonatal meconium has gained attention as a biological matrix suitable for assessing in utero exposure to xenobiotics. Meconium begins to form in the fetal intestine during the second trimester and progressively accumulates substances swallowed by the fetus, including drugs and their metabolites. Unlike maternal blood or urine, which reflect short-term exposure, meconium provides an integrated record of exposure over an extended period of pregnancy, making it particularly valuable for retrospective exposure assessment.[1,2]

Ethinyl estradiol is a synthetic estrogen widely used in oral contraceptives and other hormonal formulations. Due to its endocrine-disrupting properties, prenatal exposure to ethinyl estradiol has raised concerns regarding potential effects on fetal hormonal balance and reproductive development. Although its use during pregnancy is generally avoided, environmental exposure or inadvertent intake may still occur, underscoring the importance of monitoring fetal exposure to this compound.[3]

Sulfamethoxazole, a commonly prescribed sulfonamide antibiotic, is frequently used for the treatment of bacterial infections, sometimes during pregnancy when alternatives are limited. The drug readily crosses the placenta, and its potential association with adverse neonatal outcomes has been discussed in previous studies, particularly when exposure occurs during early or prolonged stages of gestation.[4] Despite its widespread use, data on cumulative fetal exposure remain limited.

Ibuprofen is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) worldwide. Although often perceived as safe, its use during pregnancy—especially in the later trimesters—has been associated with potential risks, including effects on fetal circulation and renal function. As ibuprofen is readily available over the counter, inadvertent exposure during pregnancy is not uncommon.[5]

While several studies have investigated maternal drug exposure using self-reported data or short-term biological matrices, limited information is available regarding the detection of these specific compounds in neonatal meconium, particularly in the context of low- and middle-income settings. Moreover, regional data from Syria are scarce. Therefore, this study aimed to evaluate neonatal meconium as a biomarker for prenatal exposure to ethinyl estradiol, sulfamethoxazole, and ibuprofen among term neonates delivered in selected hospitals in Lattakia and Damascus, using high-performance liquid chromatography (HPLC) for quantitative analysis.

MATERIALS AND METHODS

Study Design and Population

A cross-sectional study was conducted on neonates delivered in selected hospitals in the governorates of Lattakia and Damascus, Syria, during the study period. The study population consisted of 123 term neonates born in participating hospitals. Inclusion criteria were restricted to neonates with a gestational age of 37 weeks or more and without reported complications during pregnancy or delivery.

Mothers younger than 18 years of age were excluded, as were mothers diagnosed with specific medical conditions during pregnancy, including gestational hypertension, gestational diabetes, or other chronic illnesses documented in the medical records. Neonates presenting with congenital anomalies, documented intrauterine complications, or preterm birth were also excluded from the study.

Maternal and neonatal demographic and clinical data, including maternal age, place of residence, smoking status, type of delivery, gestational age, and neonatal anthropometric measurements, were obtained from hospital medical records using a standardized data collection form.

Meconium Sample Collection and Storage

Meconium samples were collected from each neonate within the first 24 hours after birth. Samples were obtained using sterile collection tubes to avoid external contamination. The collected meconium from each neonate weighed approximately 5–10 g. Immediately after collection, samples were labeled and stored at −20 °C until further laboratory processing and analysis.

Sample Preparation and Digestion

Prior to analysis, meconium samples were allowed to thaw at room temperature. Sample preparation was carried out using a wet digestion procedure to ensure efficient extraction of the target pharmaceutical compounds. Briefly, a measured amount of meconium was subjected to digestion with concentrated nitric acid (HNO_3). Microwave-assisted digestion was employed to enhance the breakdown of the organic matrix and to improve extraction efficiency. After digestion, the samples were allowed to cool and were subsequently filtered and diluted as required with appropriate solvents to obtain clear solutions suitable for chromatographic analysis.

Chromatographic Analysis

Quantitative determination of ethinyl estradiol, sulfamethoxazole, and ibuprofen was performed using high-performance liquid chromatography (HPLC). Analyses were carried out using an **Agilent 1100 HPLC system**, operated under standard analytical conditions. Separation of the target compounds was achieved using a suitable chromatographic column and mobile phase system optimized for the simultaneous detection of the three analytes. Detection was performed using the appropriate detector settings according to the physicochemical properties of each compound. Calibration curves were constructed using standard solutions of known concentrations, and quantification was based on peak area measurements.

Statistical Analysis

Statistical analysis was performed using appropriate statistical software. Descriptive statistics were used to summarize maternal and neonatal characteristics, as well as the measured concentrations of ethinyl estradiol, sulfamethoxazole, and ibuprofen in meconium samples. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Inferential analyses were conducted to explore potential associations between compound concentrations and selected maternal or neonatal variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the Study Population

The study included 123 term neonates delivered in participating hospitals in Lattakia and Damascus. Mothers were predominantly between 20 and 40 years of age, with a higher proportion residing in urban areas. Both vaginal and cesarean deliveries were represented. All neonates included in the analysis were born at a gestational age of 37 weeks or more and did not present with congenital anomalies or major complications at birth.

Detection of Target Compounds in Meconium

Ethinyl estradiol, sulfamethoxazole, and ibuprofen were successfully detected and quantified in neonatal meconium samples using HPLC analysis. The presence of these compounds in meconium indicates prenatal exposure during pregnancy.

Ethinyl estradiol was detected at low concentrations across the study population. The mean concentration was 0.329 ng/g with a standard deviation of 0.478 ng/g, reflecting generally low-level exposure with noticeable inter-individual variability.

Sulfamethoxazole was detected in meconium samples with a mean concentration of 0.554 ng/g and a standard deviation of 1.272 ng/g. While most samples showed low concentrations, higher values were observed in a limited number of cases, contributing to the observed variability.

Ibuprofen was identified at higher concentrations compared to the other two compounds. The mean concentration measured in meconium was 1.745 ng/g with a standard deviation of 2.074 ng/g, indicating low to moderate prenatal exposure and variability among neonates.

Association with Type of Delivery

Binary logistic regression analysis was conducted to examine the association between meconium concentrations of the studied compounds and type of delivery. No statistically significant association was observed between ethinyl estradiol or ibuprofen concentrations and the mode of delivery. Sulfamethoxazole showed a trend toward association; however, this association did not reach statistical significance at the conventional threshold.

Association with Neonatal Anthropometric Measurements

Linear regression analyses were performed to assess potential associations between meconium concentrations of the target compounds and neonatal anthropometric measurements, stratified by sex.

For male neonates, no statistically significant associations were observed between ethinyl estradiol, sulfamethoxazole, or ibuprofen concentrations and birth weight, body length, or head circumference.

In female neonates, sulfamethoxazole and ibuprofen concentrations showed statistically significant associations with neonatal length. Higher concentrations of sulfamethoxazole and ibuprofen were associated with variations in body length. No statistically significant associations were observed between ethinyl estradiol concentrations and neonatal anthropometric measurements in either sex.

Gestational Age

Ordinal logistic regression analysis did not demonstrate a statistically significant association between gestational age and meconium concentrations of ethinyl estradiol, sulfamethoxazole, or ibuprofen within the included term neonates.

DISCUSSION

The present study provides evidence supporting the use of neonatal meconium as a suitable biomarker for assessing prenatal exposure to selected pharmaceutical compounds, namely ethinyl estradiol, sulfamethoxazole, and ibuprofen. The detection of these substances in meconium samples collected within the first 24 hours after birth reflects fetal exposure during pregnancy, most likely during the second and third trimesters, consistent with the known timeline of meconium formation.

Ethinyl estradiol was detected at generally low concentrations in the studied samples. This finding is in line with previous reports indicating limited fetal exposure under non-therapeutic conditions, given that ethinyl estradiol is not routinely prescribed during pregnancy.[6] Nevertheless, its detection in meconium suggests that environmental exposure, unrecognized intake prior to pregnancy recognition, or residual exposure from earlier use may contribute to fetal contact with synthetic estrogens. From a biological perspective, even low-level exposure to estrogenic

compounds during critical developmental periods may interfere with endocrine signaling pathways, although the absence of significant associations with neonatal anthropometric parameters in this study suggests limited measurable impact at the observed concentrations.[7]

Sulfamethoxazole was detected in a proportion of meconium samples, with low mean concentrations but notable inter-individual variability. This variability likely reflects differences in maternal antibiotic use, timing of exposure during pregnancy, and maternal pharmacokinetics. Sulfamethoxazole is known to cross the placental barrier and has been detected previously in fetal compartments.[8] In the present study, sulfamethoxazole concentrations were not significantly associated with mode of delivery or gestational age; however, an association with neonatal length was observed among female neonates. While the underlying mechanism is not fully understood, sulfonamides have been suggested to interfere with folate metabolism, which may influence fetal growth under certain conditions.[9] The sex-specific nature of this association warrants further investigation.

Ibuprofen was detected at higher concentrations compared to ethinyl estradiol and sulfamethoxazole, which is consistent with its widespread availability and common use as an over-the-counter analgesic. Ibuprofen readily crosses the placenta, and fetal exposure has been documented in previous studies.[10] In this study, ibuprofen concentrations were not associated with birth weight or head circumference but showed a statistically significant association with neonatal length among female neonates. This observation aligns with concerns raised in the literature regarding NSAID exposure during pregnancy, particularly related to prostaglandin inhibition and its potential effects on fetal growth and vascular regulation.[11] The absence of significant associations in male neonates may indicate sex-dependent differences in susceptibility or metabolism.

Importantly, no significant associations were observed between the studied compounds and gestational age within the term population included in this study. This finding may be partly explained by the exclusion of preterm births, which limited the variability in gestational age. Additionally, the relatively low concentrations of the detected compounds may not have been sufficient to produce measurable effects on pregnancy duration.

Overall, the findings of this study are consistent with previous research supporting the value of meconium as a non-invasive matrix for retrospective assessment of prenatal exposure to pharmaceuticals.[12] The observed low to moderate concentrations of the studied compounds, along with limited associations with neonatal outcomes, suggest that while fetal exposure does occur, its measurable impact may depend on dose, timing, and individual susceptibility. Future studies with larger sample sizes, detailed exposure histories, and longitudinal follow-up are needed to further clarify the clinical relevance of prenatal exposure to these commonly used pharmaceutical agents.

CONCLUSION

This study demonstrates that neonatal meconium can be effectively used as a non-invasive biological matrix for assessing prenatal exposure to selected pharmaceutical compounds, specifically ethinyl estradiol, sulfamethoxazole, and ibuprofen. The detection of these substances in meconium samples collected shortly after birth confirms that fetal exposure to commonly used medications may occur during pregnancy, even in the absence of overt clinical indications.

The measured concentrations of ethinyl estradiol were generally low and were not associated with adverse neonatal outcomes in the studied population. Sulfamethoxazole and ibuprofen were detected at low to moderate levels, with limited but noteworthy associations observed with neonatal length among female neonates. No significant relationships were identified between the concentrations of the studied compounds and gestational age, birth weight, or head circumference within the term neonates included in this study.

Overall, the findings support the applicability of meconium analysis as a practical tool for retrospective evaluation of prenatal pharmaceutical exposure. Incorporating meconium-based monitoring into perinatal research may contribute to a better understanding of fetal exposure patterns and their potential implications for neonatal health. Further studies involving larger cohorts and detailed exposure assessment are recommended to clarify the long-term significance of prenatal exposure to these commonly used pharmaceutical agents.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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