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Feasibility of a non-invasive retrospective determination of Methylmercury Elimination During Pregnancy

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Short Report

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Abstract

Prenatal methylmercury (MeHg) exposure remains a priority health concern, particularly among fish eating populations. Yet, the kinetics of methylmercury (MeHg) metabolism and elimination in pregnant women and the fetus remain poorly understood. Measurements in non-pregnant women and men show that a wide variation in MeHg elimination rates can exist ($t_{1/2}$ <30 to > 120 days), whereby 'slow eliminators' will be prone to accumulating the highest MeHg levels. Because MeHg transfer across the placenta is rapid, determinations of MeHg kinetics in pregnant women will directly inform the susceptibility of the fetus to excess MeHg exposure from fish consumption. Here, we assess the feasibility of determining MeHg exposure profiles and elimination rates in fish-eating pregnant women via a non-invasive longitudinal Hg analysis using laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) of single strands of hair collected postnatally. Hair profiles completed for four subjects showed elevated Hg levels in three fish eaters compared to a non-fish eater. Fish-eating pregnant women were identified by characteristic profiles of peaks and decay of Hg over ~ 240 days spanning the 1st to 3rd trimester. MeHg elimination rates extracted from the Hg profiles showed a wide range of half-lives between individual women ($t_{1/2}$ = 25 to > 130 days). Elimination rates were also seen to increase two-fold from 1st to 3rd trimester in two individuals. This study establishes that individualized determinations MeHg elimination kinetics in pregnant women can be readily made and warrants further investigation to ultimately contribute to strategies to minimize fetal exposure.

1. INTRODUCTION

Exposure to MeHg through consumption of fish continues to pose a health risk to many populations. The developing nervous system is a highly susceptible target for MeHg toxicity and thus exposure to the fetus is of the greatest concern. However, variable outcomes in a number of epidemiological studies of prenatal MeHg exposure within mother-child cohorts in fish and seafood eating populations have led to uncertainty in advising the public on mercury risks associated with fish consumption [1–3]. Much of the uncertainty stems from the fact that MeHg metabolism and elimination rate can vary widely from individual to individual [4–6]. Approaches to identify maternal-fetal susceptibility to MeHg toxicity are therefore difficult and lacking. Thus, identifying what makes a pregnant woman prone to accumulate MeHg with fish consumption remains a significant challenge and important human health concern.

A critical factor contributing to a toxic outcome from MeHg exposures is the level of MeHg that accumulates (i.e. the body burden) with routine eating of fish meals. The slow elimination rate (long half-life) of MeHg ($t_{1/2}$ ~ 45 days) is the determining factor of body burden. Ingested MeHg is absorbed very efficiently in the intestine with ~ 95% of the dose typically being taken up and distributed peripherally via the bloodstream [7]. MeHg undergoes rapid transport and equilibration between blood and organs [7], including the placenta and fetus. After an individual dose, MeHg levels in blood subsequently resolve to a slow steady rate of decline that is dictated by the overall elimination rate of MeHg from the body, a process that can be monitored retrospectively along the length of growing strands of hair [4, 8, 9]. Controlled studies of MeHg elimination rates in adults (non-pregnant) show a range from $t_{1/2}$ = 30 to > 120 days, demonstrating the existence of fast and slow MeHg metabolizers (reviewed in [10]). To date, there are essentially no controlled studies on MeHg elimination rate in pregnant women.

We have developed a non-invasive method and protocol to quantify MeHg metabolism and elimination in people [4, 5]. Briefly, subjects consume three fish meals at one-week intervals. After 60 days of elimination, samples of hair are collected for longitudinal Hg measurement using laser ablation-ICP-mass spectrometry. The profile of Hg along the hair segment proximal to the scalp reflects the blood Hg levels over time, which can be used calculate an elimination rate from the decline in Hg seen subsequent to the fish meals [4, 5]. The sensitivity of this method permits detection of MeHg originating from individual fish meals [5].

In this study, we adapted this previously established, non-invasive method of MeHg elimination rate determination to fish-eating pregnant women. We find the method is highly effective in revealing a MeHg exposure profile and determining kinetics that can distinguish pregnant women with different susceptibilities to accumulate MeHg.

2. METHODS

All methods and procedures were reviewed and approved by the University of Rochester Institutional Review Board on human subjects research. Participants were included if they were pregnant or recently pregnant, aged 18–50 years old, in generally good health based on self-assessment, and had at least 10 cm of hair. Patients were excluded if they had a twin gestation, known gastrointestinal or renal disease likely to alter MeHg excretion or metabolism, diminished mental capacity or inability to speak or read English, and less than 10 cm of hair. Hair samples from 30 post-partum women were collected. A screening questionnaire was used to confirm whether or not they ate any fish during their pregnancy as well as type and frequency of fish consumption. For each subject, ten to 15 hair samples were collected with manual, direct pulling out by the roots from the posterior region of the head (crown) and stored in zip-lock bags. Following collection, hairs were mounted on double stick tape (Scotch Brand) on a microscope slide and stored at room temperature. Four subjects were selected for this feasibility analysis: 3 fish eaters and 1 non fish eater. The fish eaters were selected based on higher (S3 and S23) or lower (S7) reported levels of fish consumption and one subject who reported no fish consumption (S13) using laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS, Agilent Technologies, 8900 ICP-MS) housed at the Trace Element Analysis (TEA) lab at Dartmouth College. Parameters of laser power, gas flow rates, dwell time and acquisition time were optimized with assistance from the TEA facility staff. Methods of Hg determination followed previously described protocols [4, 5, 11]. Briefly, ablation of 50μm spots was carried out at 333μm intervals along a 10cm length of the initial segment of hair closest to the scalp. Hair growth rate used for kinetic determinations was assigned the average of 1.0 cm per month [12, 13]. Therefore, ~ 10cm of the initial segment of hair was analyzed to cover the period of pregnancy and approximately one month prior. The natural ^{202}Hg isotope was detected and normalized to the amount of hair sampled in the ablation event by detecting ^{34}S in parallel and determining the Hg/S ratio. Hg/S ratio values in hair were converted to part per million (ppm) values based on LA-ICP-MS analysis of a hair standard reference material performed in parallel (IAEA 86, 0.573 ppm Hg total [14]). Visual spikes in Hg revealed instances of MeHg exposure presumably linked to a fish meal. The subsequent decline in Hg concentration over time was used to evaluate elimination rates for the fish consumption event. Results from subject S13, who reported no fish or seafood eating, yielded a very low level of Hg which remained ‘flat’ across pregnancy (See Results). This was assumed to represent a background level of Hg exposure. The average Hg value across this hair was then used to do a background subtraction from the Hg determination of the other three subjects (S3, S7, S23). Elimination

rate (k_{el} in days^{-1}) was then determined by linear regression analysis of Hg concentration over time in a semi-log plot. The elimination rate was used to estimate a biological half-life ($t_{1/2}$ = 0.693/ k_{el}) in units of days.

3. RESULTS

Longitudinal Hg hair profiles, expressed in ppm Hg, were completed for four subjects and showed detectable differences between the fish eaters (S23, S7, S3) and a non-fish eater (S13), with an overall elevated level of Hg seen across pregnancy in the hair of the fish eating subjects. By their own recollection, both subjects S3 and S23 reported consumption of canned tuna 2–3 times weekly during pregnancy, whereas S7 reported significantly less fish or seafood consumption. S23's Hg profile showed definitive Hg peaks and declines, which were interpreted as events of fish meal consumption followed by MeHg elimination between fish meals. The elimination rate, expressed as half-life, was calculated from regions where Hg decline over time was obvious (denoted with yellow filled circles in Figs. 1A-C). These rates showed a remarkable variability between subjects and, notably, across time within each subject. Subject S23 had a $t_{1/2}$=25–50 days across pregnancy (Fig. 2B), with faster MeHg elimination occurring in the 3rd trimester as compared to the 1st trimester. Subject S3 had a relatively fast and consistent rate of $t_{1/2}$=25–32 days (Fig. 2A). Whereas Subject S7 showed a considerably slower overall elimination with $t_{1/2}$=63–131 days (Fig. 2C), this subject also demonstrated a faster elimination rate in 3rd trimester compared to 1st trimester. Subject S13, who claimed no fish eating, showed an essentially flat line of low Hg levels across pregnancy (gray filled circles in Fig. 1A-C), and was interpreted to represent a background level of Hg exposure.

4. DISCUSSION

We demonstrate the feasibility and utility of a non-invasive, relatively rapid method to individually evaluate MeHg elimination rate in women at time points across pregnancy. Applying this method to a wider range of subjects in a research context will be make it possible to definitively relate maternal MeHg exposure to prenatal fetal exposure and ultimately to developmental outcomes in children. This will alleviate the considerable uncertainty intrinsic in conventional epidemiological studies where maternal MeHg dose is determined through diet recalls or single time-point Hg determinations in blood or hair that introduce considerable error [15]. The present method will advance such studies by resolving the precise gestational timing of MeHg exposures, in addition to deriving an accurate determination of cumulative exposure enabling more robust associations to be made between maternal body burden and fetal exposures and outcomes.

The results also point to an intriguing trend where it appears that MeHg elimination increases as pregnancy progresses from 1st to 3rd trimester. While this needs to be substantiated with many more subjects, such a trend points to a favorable physiology that would protect the fetus. It is reasonable to speculate that such a shift in the MeHg toxicokinetics may stem from physiological changes that similarly affect drug metabolism [16] [17]. Alternatively, increases in MeHg kinetics may evolve from changes in gut microbiome diversity and/or abundance that parallel pregnancy advance [18]. Gaining more evidence for these plausible mechanisms controlling MeHg toxicokineics will lead to more concrete advice for pregnant women on fish consumption and limiting risk of MeHg exposure. Another exciting avenue to explore is to examine MeHg profiles in the newborn's hair in parallel with the mother's hair. Conceivably, fetal MeHg exposure in third trimester could be determined directly from hair captured from the newborns scalp at or soon after delivery. Comparison between maternal

and fetal MeHg elimination profiles extrapolated from the respective hair Hg profiles would unambiguously define whether or not the fetus becomes a ‘reservoir’ for MeHg coming from maternal fish eating. Nonetheless, this latter application would be limited by the fact that roughly 30% of newborns have no scalp hair at delivery.

This study has several limitations. First, despite demonstrating feasibility, the limited number of subjects examined precludes any significant conclusions regarding the variation in rates seen between and within subjects. In addition, human hair growth rate is known to be variable between people [10], which is not accounted for in the current study design. The hair growth rate is the kinetic basis for the determinations in this method. Where the precise timing of fish meals is known, hair growth rates can be determined directly by measuring the length of hair grown between fish meal events [4]. Therefore, future studies will benefit from a study design where the timing of fish meals can be accurately recorded by the subject leading to more rigorous kinetic analyses. One possibility is to have subjects document meals with a time-stamped image e.g. with a smartphone picture at the time of eating the meal.

5. CONCLUSION

We report a robust method for determining individualized metabolism and elimination kinetics of MeHg in pregnant fish-eating women is now feasible. Pregnant women can demonstrate highly variable MeHg kinetics between individuals and within an individual over gestation, with the possibility that MeHg elimination increases in the third trimester. This methodological advance will facilitate future studies aimed at resolving factors that influence, and potentially minimize, maternal MeHg exposure from fish.

DECLARATIONS

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The datasets generated during and/or analyzed during the current study are available from the Corresponding Author upon request.

All methods and procedures were reviewed and approved by the University of Rochester Institutional Research Subjects Review Board for human subjects research (RSRB #70789).

Author Contribution

All authors contributed to the study conception and design. Subject consenting and hair sample collection was performed by E.J. under the supervision of L.T. Hair analysis and data collection was performed by T.P. and B. J. Data analysis was performed by M.R. The first draft of the manuscript was written by M.R. and and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the Corresponding Author upon request.

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Figures

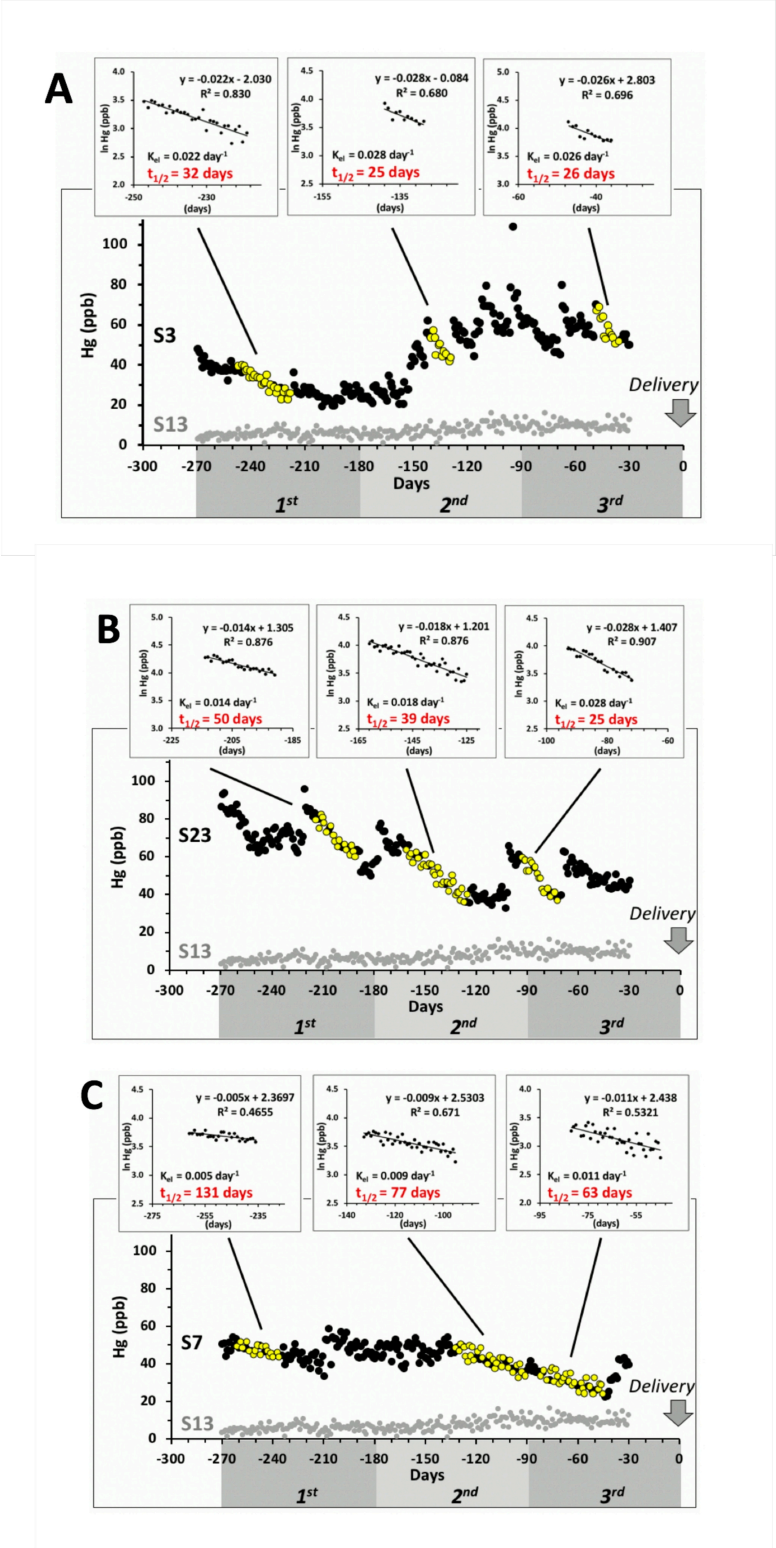


Figure 1

Variation in MeHg elimination rates in pregnant women. Hg (in part per billion, ppb) in hair versus time plots for fish-eating (A, Subject 3; B, Subject 7 and C, Subject 23) and a non-fish eating woman (Subject 13, in gray filled circles in A-C) over approximately 240 days of pregnancy spanning 1st to 3rd trimester. Periods of elimination (yellow filled circles) after an apparent fish meal "spike" in Hg are indicated. MeHg elimination rate (k_{el}) and half-life ($t_{1/2}$) within 1st, 2nd, and 3rd trimester for each subject derived from semi-log plots shown in insets.