**Meconium stained amniotic fluid and offspring long-term neurological health- a population based cohort analysis**

Ron MATALONa\* BSc, Tamar WAINSTOCKb PhD, Asnat WALFISCHd MD, and Eyal SHEINERC MD PhD

Author affiliations

*aThe Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.*

*bDepartment of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

*c Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel.*

*dDepartment of Obstetrics and Gynecology, Hadassah Mt, Scopus Medical Center, Jerusalem, Israel.*

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***Authors e-mail addresses:***

Tamar Wainstock: wainstoc@bgu.ac.il

Eyal Sheiner: sheiner@bgu.ac.il

Asnat Walfisch: asnatw@bgu.ac.il

***Corresponding author:***

Ron Matalon, BSc

The Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Ben-Gurion University Medical School, Soroka University Medical Center, 151 Izak Rager Ave., Beer-Sheva 84101, Israel.

Phone: +972-54-2204085

Email: ron.matalon@gmail.com

**ABSTRACT**

**Objective:** This study aimed to investigate the possible impact of meconium-stained amniotic fluid (MSAF), recently found not to be sterile as previously thought, on the occurrence of neurological-related hospitalizations in the offspring throughout childhood and adolescence.

**Methods:** In this population-based cohort analysis, all singleton deliveries occurring between 1991and 2014 at a single tertiary medical center were included. Fetuses with congenital malformations were excluded. A Kaplan-Meier survival analysis was constructed for evaluation of cumulative hospitalization rate due to neurological morbidity (such as autism, cerebral palsy, developmental disorders etc.) over the 18 years of follow-up, and a Cox proportional hazards model was used to study the independent association between MSAF and neurological morbidity while controlling for potential confounders.

**Results:** During the study period, 242,342 deliveries met the inclusion criteria. A total of 7,543 hospitalizations due to neurological-related morbidity were documented with a rate of 3.2% (1,152) in children exposed to MSAF as compared with 3.1% (6,391) in the unexposed group (odds ratio 1.05, 95% CI 0.98–1.12, *p* = .149). The survival curve showed a comparable cumulative hospitalization rate in the MSAF-exposed group compared to the unexposed group (log rank *p* = .349). The Cox analysis, controlled for maternal diabetes and hypertension as well as for gestational age and maternal age, demonstrated MSAF exposure ***not to be*** an independent risk factor for neurological-related hospitalizations during childhood in the offspring (adjusted HR = 1.025, 0.962–1.092). This was also true when analyzed for preterm deliveries (<37 weeks) only (adjusted HR = 1.194, 0.906–1.572).

**Conclusion:** Fetal exposure to MSAF, whether at term or preterm, does not appear to be an independent risk factor for neurological-related hospitalizations in the offspring throughout childhood and adolescence.

**Introduction:**

Meconium passage is a normal, nonpathological event usually occurring within 24–48 hours after birth.1 However, one of the severe signs of fetal compromise is exposure to meconium-stained amniotic fluid (MSAF), observed in 5% to 20% of labors, which may lead to significant morbidity in offspring.2 Despite previous assumptions that the first-pass meconium is sterile,3 MSAF was recently found not to be sterile as previously thought.4

MSAF is significantly more common in post-term deliveries as compared to term deliveries (14.9% and 25.9%, respectively).5 It was also found that the longer the duration of labor, the higher the frequency of MSAF.6 Other risk factors associated with MSAF are older maternal age, multiparty and lack of prenatal.7

Studies have found that MSAF can lead to several pregnancy complications, not only in high-risk pregnancies but also in low-risk pregnancies.8 MSAF was found as a risk factor for intrauterine fetal death,9 intrapartum fetal death,10 abnormal fetal heart rate tracings and low Apgar scores at 1 minute.9 MSAF was also found as a risk factor for meconium aspiration syndrome, neonatal hypoxic-ischemic encephalopathy, neonatal sepsis and seizures.11

The long-term implications of MSAF exposure are varied. Meconium aspiration syndrome, one of the major impacts of MSAF, has long-term pulmonary sequelae that include airway obstruction, hyperinflation, elevated closing volumes and airway hyperreactivity.12 Interestingly, the presence of meconium during labor was associated with lower rates of long-term infections13 and dermatological morbidity in the offspring,14 emphasizing a possible role of meconium in the maturation of the immune and microbial systems of the newborn.

Another critical outcome that, to the best of our knowledge, has not been investigated thoroughly is the association between exposure to MSAF and long-term neurological morbidity. We aimed to determine whether MSAF exposure during labor may adversely affect the long-term neurological health of the offspring.

**Materials and methods**:

In this retrospective population-based cohort analysis, we aimed to investigate the impact of MSAF on the occurrence of neurological-related hospitalizations of the offspring throughout childhood and adolescence. The study population consisted of all singleton deliveries occurring between the years 1991 and 2014 at the Soroka University Medical Center (SUMC), a tertiary hospital in the Negev (southern part of Israel). This hospital serves approximately 1,272,100 residents living in the Negev region, the fourth largest in Israel in terms of population size and very diverse in terms of population characteristics and forms of settlements.15

The study protocol was approved by the SUMC institutional review board, and informed consent was exempt due to the nature of the study design.

The study population consisted of all singleton deliveries, divided into 2 groups by the independent variable—exposure to MSAF. A comparison was performed between offspring born with or without exposure to MSAF. Fetuses with congenital malformations were excluded.

Data were collected from 2 data sets. The first, a computerized perinatal database of the obstetrics and gynecology department at SUMC, included obstetrical and general maternal, fetal and neonatal data documented during delivery by the attending physician and hospital staff.

The second, a data set of all pediatric hospitalizations at SUMC, included medical diagnoses and demographic characteristics according to *ICD-9* codes. Long-term neurological morbidity was predefined by a pediatrician as one or more of the *ICD-9* diagnoses detailed in the code list of the Supplement Table, which includes various neurological pathologies. The 2 data sets were cross-linked and merged. To ensure data accuracy, the information was routinely approved and tested by experienced medical secretaries before being entered in the database. The follow-up time was defined as time to event (first neurological-related hospitalization) or until censoring occurred (death of the child, end of the study period or the child’s reaching18 years of age).

Background and dependent variables were compared between the 2 study groups in univariable analysis. The tests used included the *t* test or Mann-Whitney U test for continuous variables according to their distribution and the chi-square test for categorical variables. Calculation of cumulative incidence rates was performed with the Kaplan-Meier method, using the log-rank test to determine significant differences between the groups.

A Cox regression analysis was used to control for confounders. Potential confounders were taken into account based on the univariable analysis as well as on the clinical significance of the variables. The final model was chosen based on the best fit and the minimal -2log likelihood. All the models and statistical analysis were conducted and performed using STATA (version 12 or higher) or SPSS (version 23 or higher) software.

**Results:**

During the study period, 243,725 deliveries met the inclusion criteria; 35,897 of the cohort (14%) constituted the exposed group (MSAF-exposed infants), while the rest of the cohort (*n* = 207,828) constituted the comparison, or “no MSAF,” group.

Table 1 shows the demographic characteristics and immediate perinatal outcomes of the exposed and unexposed groups. The exposed MSAF group was characterized by slightly older mothers (28.65±5.9 years vs. 28.08±5.8 years, *p* < .001), longer gestational age (mean 39 5/7±2 vs. 38 6/7±2 weeks of gestation) and a higher mean birth weight (3,281±486 gr vs. 3,192±514 gr).

Total neurological morbidity up to the age of 18 years was similar among children exposed to MSAF (3.2% vs. 3.1%, OR = 1.048; 95% CI 0.98–1.12; Table 2). No significant difference was found in the specific neurological pathologies (CP, PDD etc.) between the two groups. Moreover, no difference in cumulative incidence of neurological hospitalizations was found between the exposed and unexposed groups, as demonstrated in the survival curves (Figure 1).

The Cox analysis, controlled for maternal diabetes and hypertension as well as for gestational age and maternal age, demonstrated MSAF exposure ***not to be*** an independent risk factor for neurological-related hospitalizations during childhood in the offspring (adjusted HR = 1.025, 0.962–1.092; Table 3). This was also true when analyzed for preterm deliveries (<37 weeks) only (adjusted HR = 1.194, 0.906–1.572).

**Discussion:**

Intrauterine extra-alimentary exposure to the infantile gut microbiome is frequently associated with microbial invasion of the amniotic cavity, resulting in increased cytokine production. Meconium can stimulate vasoconstriction of placental veins, thereby precipitating brain-damaging hypoxemia. Therefore, we assumed that MSAF would be associated with an increased occurrence of neurological-related hospitalizations in the offspring throughout childhood and adolescence. However, in this large population-based cohort study, MSAF exposure was not found to be an independent risk factor for neurological-related hospitalizations during childhood in the offspring.

Although our study did not find any long-term impact on neurological morbidity, other studies have found that MSAF has a significant short-term impact on the offspring, such as low Apgar scores, intrapartum fever,16 operative vaginal and cesarean17 and meconium aspiration syndrome (MAS).18 The fact that MSAF has no impact on long-term neurological morbidity of offspring may be due to several reasons.

Studies have found an association between the gut microflora and the body’s ability to deal with pathogens.19,20 Early exposure to gut microbiota has been found to reduce the risk of long-term inflammatory disease, which is reinforced by the fact that children who are born by cesarean and not in vaginal delivery are more likely to suffer from asthma, celiac disease, diabetes type 1 and neurological morbidity.21–24

 Though MSAF is assumed to be an adverse reactant, recent studies have questioned this assumption and presented the meconium as a protecting factor against long-term infectious13 and dermatological14 morbidity. Therefore, it can be assumed that meconium has a positive association with the newborn, and the stigma against meconium as a negative long-term cause is not necessarily accurate.

Also, although neurological development is an ongoing process that continues long after birth, it can be assumed that fast and effective treatment in offspring exposed to MSAF helps prevent neurological morbidity and future damage. An adequate treatment that includes supportive therapy such as oxygen supplementation, mechanical ventilation and intravenous fluids, availability of surfactant, inhaled nitric oxide, high-frequency ventilators and extracorporeal membrane oxygenation reduce the morbidity and mortality associated with MAS.25

Another hypothesis that may explain the lack of association between MSAF and long-term neurological morbidity is the fact that MSAF is associated with peripartum stress such as hypoxia.26,27 The peripartum stress through MSAF delivery activates the hypothalamic-pituitary-adrenal (HPA) axis to produce stress hormones such as cortisol.28 Stress-hormone production helps the compensatory mechanism to control the stress situation by supplying energy via protein catabolism, gluconeogenesis and glucogenesis. It can cause hyperglycemia, hyperlipidemia and blood, bone, muscle, cardiovascular, gastrointestinal, endocrinal and central nervous system changes.29,30 Studies have shown that corticosteroid treatment can reduce and even improve neurological morbidity in offspring.31,32 Thus, the increase of the stress-related hormones may reduce adverse neurological outcomes.

The main strength of our study is the population on which it was conducted. The study consisted of a large number of patients (more than 200,000) in SUMC, which is the only tertiary medical center providing comprehensive care for the entire population of the Negev region. This fact prevented loss of information and follow- up data and allowed long-term follow-up of offspring health and hospitalizations that occurred during childhood and adolescence. Furthermore, we were able to control for many parameters and potential confounders regarding pregnancy and delivery.

However, our study has some limitations. First, immigration outside the Negev region or health care in a different hospital are a reasonable possibility of a loss of follow-up. However, it is reasonable to assume that differences in immigration are unlikely to be based on exposure (or not) to MSAF.

Another important limitation is the fact that we do not have data on the density of meconium within the amniotic fluid. Additionally, we could not distinguish the onset of meconium passage during labor (i.e, primary meconium that was already present at the time of membranes rupture or secondary meconium).

In conclusion, our study did not find MSAF exposure to be an adverse reactant on neurological morbidity, and it does not appear to be an independent risk factor for long-term neurological hospitalizations in the offspring throughout childhood and adolescence.

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**Table 1:** Maternal characteristics of the study population.

**Table 2:** Incidence of neurological hospitalizations of the offspring in MSAF-exposed and unexposed groups.



**Table 3**: Cox model to predict long-term neuropsychiatric morbidity in offspring after exposure to meconium-stained amniotic fluid.

**Figure 1:** Kaplan Meier survival curve for cumulative incidence of neurological morbidity in offspring of patients with and without exposure to meconium-stained amniotic fluid; log rank *p* = .349.

