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ORIGINAL ARTICLE

Maternal smoking and fetal lung signals – an *in utero* MRI investigation

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ABSTRACT

Objective To investigate whether fetal lung signals and fetal lung signal progression over gestation observed on magnetic resonance imaging are different in mothers who reported smoking during pregnancy compared with nonsmoking controls.

Method Cross-sectional retrospective study of 100 consecutive singleton pregnancies that underwent magnetic resonance imaging. Fetal lung–liver signal intensity ratios of 18 fetuses of mothers who reported smoking during pregnancy were compared with 82 fetuses of nonsmoking controls.

Results Average gestational age at magnetic resonance imaging was 26.4 ± 5.2 weeks (Range 18.4–38.2 weeks). Cases reported smoking between 2 and 15 cigarettes per day. The mean number of cigarettes per day for cases was 9.2 ± 3.4. Mean fetal lung-liver signal intensity ratios did not differ significantly between the two groups ($p = 0.8$). They showed a linear increase with gestational age ($r^2 = 0.3$). Multiple regression analysis of lung–liver signal intensity ratios using gestational age and smoking status as predictors revealed a significant influence of gestational age ($p < 0.0001$) but not maternal smoking status ($p = 0.8$) on fetal lung–liver signal intensity ratios.

Conclusions Fetuses of mothers who reported smoking during pregnancy show similar lung signals and lung signal progression over gestation on magnetic resonance imaging as nonsmoking controls.

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INTRODUCTION

There is extensive epidemiologic and experimental evidence that demonstrates unfavorable pulmonary outcomes in the offspring of mothers who smoke during pregnancy.[1] Maternal smoking during pregnancy is associated with a significant increase in respiratory symptoms and a decrease in lung function in neonates and infants.[2–6] The molecular mechanisms underlying these associations are not fully understood. There is now growing evidence that maternal smoking during pregnancy affects fetal lung development *in utero*, eventually leading to an impaired lung function and an increased risk of respiratory illness after birth.[7]

The effects of maternal smoking on the fetus are due to indirect fetal exposure to components of cigarette smoke via placental transfer.[8] Tobacco smoke contains over 4000 chemical constituents and additives including known carcinogens, toxic heavy metals and many chemicals untested for growth related toxicity.[9] Although the exact mechanism of how most of these toxins affect the fetal lung is uncertain, their main target appear to be airway epithelial cells undergoing maturation and/or rapid proliferation.[10] Nicotine in particular plays a major role.[8] Several studies have shown that nicotine can permanently affect the developing lung such that its final structure and function are considerably affected.[7] In animal models nicotine exposure has shown to decrease pulmonary elastin content, decrease the numbers of alveoli, lead to greater alveolar volumes, increase presence of alveolar wall fenestrations and decrease the surface available for gas exchange as seen in emphysema.[8] However, studying the effects of maternal smoking on the human fetal lung *in vivo* is challenging and data scarce.

A promising magnetic resonance imaging (MRI) approach to investigate fetal lung development *in vivo* is to assess the signal

intensity characteristics of the fetal lung by evaluating the signal intensity ratio between lung and liver (LLSIR).[11–13] Because of the potential of MRI to characterize the chemical and structural composition of different tissue types, several attempts have been made to use signal intensity measurements on different sequences to assess developmental changes associated with biochemical maturation processes.[11,14–16] Our group has been able to demonstrate that LLSIRs increase over several gestational weeks on T2-weighted images, reflecting a brightening of the lung, which can be related to a variety of physiological processes during lung development such as to the increase of future airspaces and reduction of pulmonary interstitial tissue and to the increase of lipid and protein containing surfactant.[11,12] We were also able to demonstrate a significant increase in LLSIR after antenatal corticosteroid treatment for induction of lung maturation on T2-weighted images, which most likely also reflects changing properties of the fetal lung parenchyma.[17]

In the present study, we investigated whether LLSIRs and LLSIR progression over gestation are different between mothers who reported smoking during pregnancy compared with nonsmoking controls. We hypothesized that maternal smoking could lead to structural and biochemical changes of fetal lung parenchyma, which can be visualized by MRI on T2-weighted images.

METHODS

Subjects

Approval for this study was obtained by the institutional review board of the Medical University of Vienna. Clinical data were obtained retrospectively from files of the Department of Obstetrics and Feto-maternal Medicine, Medical University of Vienna General Hospital. Included fetuses had no thoracic or lung abnormalities and demonstrated appropriate growth and biometric data for the respective gestational age at time of MRI confirmed by previous ultrasound. Furthermore, amniotic fluid volume was normal and there was no evidence of premature rupture of membranes. A total of 100 consecutive singleton pregnancies that underwent MRI at the University Clinic of Radiodiagnostics, Medical University of Vienna General Hospital between September 2006 and June 2008, and fulfilled these criteria for inclusion were evaluated. Referral diagnosis for MRI included fetal abnormalities of the central nervous system or fetal head ($n=50$), the gastrointestinal tract or fetal abdomen ($n=11$), the genitourinary tract ($n=8$), the fetal heart ($n=7$), the fetal extremities ($n=3$) and abnormalities of the placenta ($n=2$) that had been suspected on ultrasound. Furthermore, our sample included mothers that underwent MRI because of maternal disease or a clinical history of fetal complications in previous pregnancies ($n=19$). Informed consent for MRI was obtained prior to imaging. Gestational age was calculated based on last menstrual period or, in equivocal cases on results of ultrasound measurement of crown–rump length in the first trimester. Fetal LLSIR of 18 mothers who reported smoking during pregnancy were compared with 82 fetuses of nonsmoking controls. Information on maternal smoking status and number of cigarettes smoked at time of MRI was obtained retrospectively from clinical files.

Magnetic resonance imaging

Studies were performed on a 1.5 Tesla superconducting unit (Philips Gyroscan Intera, Philips Medical Systems, The Netherlands), in conjunction with a five-channel, phased array SENSE cardiac coil. The subjects were scanned in the supine or lateral decubitus position, without any kind of sedation. After localizing the fetus using steady-state free precession (SSFP) multiplanar scout images the coil was systematically (re) positioned with the fetal thorax and fetal abdomen situated in the center of the five coil elements. The imaging protocol included multiplanar T2-weighted, turbo spin echo (TSE) sequences of the fetal thorax with two different echo times (TE = 100 ms and 140 ms). Underlying radio frequency inhomogeneities were removed using the coil sensitivity calibration scan. During the course of the study, the sequences were constantly optimized (T2-weighted TSE sequences: echo time 100–140 ms, shortest repeat time 15 900 ms, field of view between 230 × 230 and 300 × 300 mm, slice thickness ranging from 3.0 to 4.0 mm with 0.3 and 0.4 mm intersection gap, in-plane resolution ranging from $0.9 \times 1.4 \times 3\,mm^3$ to $0.9 \times 1.4 \times 4\,mm^3$). The acquisition times varied between 15 and 21 s, the total examination time did not exceed 40 min. Images were networked through a clinical picture archiving and communication system and also transferred to a DICOM-compliant personal computer.

Image evaluation

Magnetic resonance images were evaluated on a picture archiving and communication system for clinical reporting and on a personal computer with the open source IMAGE-J software package (Image J 1.38x, Wayne Rasband, National Institutes of Health, USA, http://rsbweb.nih.gov/ij/index.html) for study purposes. The mean signal intensity values for the right lung and liver were assessed on the best coronal images of sequences with echo times of either 100 or 140 ms, on the slices that displayed the fetal lung, liver, and stomach at the same time. Echo times for the evaluated slices did not differ between the two time points for one fetus. The intrapulmonary region of interest for the lung was set as large as possible, omitting the hila and anatomical border zones. The region of interest of the liver was set to the maximal assessable size, avoiding major blood vessels and the border zones on the same coronal slice (Figure 1). To compensate for interpatient and interexamination variations of tissue-specific relaxation times and the different distances between the receiver coil and the fetal organs in each patient, LLSIRs were calculated. The images were interpreted and evaluated by the first author or a co-author.

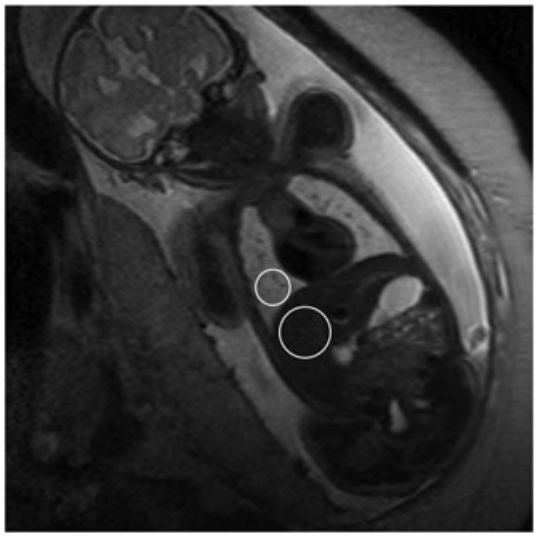

Figure 1 Coronal T2-weighted image of a fetus at 32 gestational weeks. The region of interest for signal intensity measurement in the lung and in the liver are depicted (white circles)

Statistical analysis

Power and sample size were calculated using nQuery Advisor 7.0 (Statistical Solutions, Saugus, MA). An *a priori* power analysis was performed indicating that 18 patients per group are needed to detect a difference in LLSIRs of 0.8 with a power of 80%. Post-hoc power analysis revealed a power of 96% to detect a difference in LLSIR of 0.8. All statistical analyses were conducted using SPSS 17.0.1 (SPSS Inc., Chicago, IL). Metric data like maternal age or fetal crown–rump length were described using means + / – standard deviations. Nominal data are presented using percentages. For the comparison of fetuses from smoking and nonsmoking mothers unpaired *t*-tests or Welch tests depending on the homogeneity/heterogeneity of variances were used for metric and chi square tests for nominal data. Additionally, Pearson correlations and linear regression analysis were used to assess the impact of maternal smoking status and gestational age on LLSIRs. Furthermore, multiple regression analysis was performed using gestational age and smoking status as predictors. *P* values of $p \leq 0.05$ were considered to indicate significant results.

RESULTS

Patient characteristics are shown in Table 1. Average gestational age at MRI was 26.4 ± 5.2 weeks (Range 18.4–38.2 weeks). Cases reported smoking between 2 and 15 cigarettes per day. The mean number of cigarettes per day was 9.2 ± 3.4. LLSIR showed a linear increase with gestational age (LLSIR = 0.011 × gestational age + 0.419, $r^2 = 0.256$, Figure 2). There was no significant difference in mean LLSIR between fetuses of mothers who reported smoking during pregnancy and those of nonsmoking controls (2.47 ± 0.90 vs 2.42 ± 0.76, $p = 0.8$, Figure 3). Multiple linear regression analysis with gestational age and maternal smoking status as predictors revealed a significant influence of gestational age ($p < 0.0001$) but not maternal smoking status ($p = 0.8$) on LLSIR.

Table 1 Patient characteristics. *N* (%)[1] or mean (SD)[2]

Characteristics	Smoking	Nonsmoking	*P*-value
Included patients	18[1]	82[1]	—
Age (years)	29.6 (8.1)[2]	29.4 (6.0)[2]	0.9
Cigarettes per day	9.2 (3.4)	0.0 (0.0)	—
Parity	1.5 (1.3)[2]	1.6 (1.0)[2]	0.8
BMI	22.6 (3.3)[2]	24.6 (5.0)[2]	0.1
Gestational age (weeks)	26.4 (5.6)[2]	26.4 (5.2)[2]	1.0
Fetal gender			
Male	9 (50)[1]	41(50)[1]	1.0
Female	9 (50)[1]	41(50)[1]	—
CRL (mm)	194.9 (48.7)[1]	200.9 (48.0)[1]	0.6

N, number; SD, standard deviation; CRL, crown–rump length.

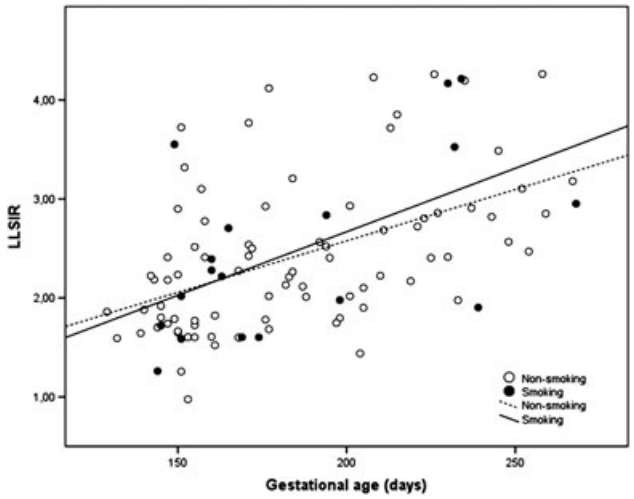

Figure 2 Fetal lung and liver signal intensity ratios and gestational age in days. The gray solid line represents the linear regression line for mothers that reported smoking during pregnancy ($r^2 = 0.3$); the gray dashed line represents the linear regression line for non-smoking controls ($r^2 = 0.2$)

DISCUSSION

In this *in vivo* imaging study of the fetal lung no difference was found between LLSIRs and LLSIR progression over gestation between mothers who reported smoking during pregnancy and nonsmoking controls. Our data suggest that possible structural or biochemical changes of the developing lung because of maternal smoking cannot readily be visualized by measuring fetal lung signals on T2-weighted images.

Maternal smoking during pregnancy can severely affect critical stages of lung development. In animal models exposure to the components of cigarette smoke has shown to decrease

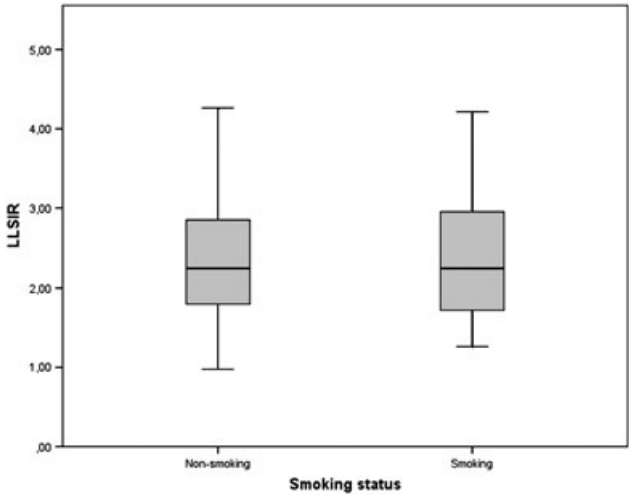

Figure 3 Box plot of fetal lung and liver signal intensity ratios of mothers that reported smoking during pregnancy and nonsmoking controls

pulmonary elastin content, decrease the numbers of alveoli, lead to greater alveolar volumes, increase presence of alveolar wall fenestrations, and decrease the surface available for gas exchange as seen in emphysema.[8] MRI is commonly used to investigate the developing lung in human fetuses *in vivo*. For this purpose it has proven to be an efficient, noninvasive, and harmless method.[12] It has successfully been used to visualize structural and biochemical changes on T2-weighted images during fetal development[11,12,18] and after antenatal corticosteroid treatment for induction of lung maturation.[17] However, in this study and an earlier study examining fetal lung volumes[19] we were unable to demonstrate any clinically relevant effect of maternal smoking on fetal lung development *in utero* using MRI. Our findings do not rule out that smoking during pregnancy results in structural or functional changes of the developing lung such that exposed infants have altered airways at birth. Although a paucity of data suggests the presence of abnormal changes in fetuses of smoking mothers, our results emphasize that fetal MRI cannot easily detect the impact of smoking on fetal lung development *in utero*. Because fetal MRI is sensitive enough to reliably identify cases of pulmonary hypoplasia,[20–22] this further suggests that smoking-related fetal lung structure alterations might be too subtle to influence fetal lung signals at 1.5 Tesla. Of note, our study was designed to detect a difference of LLSIR of 0.8, which we consider to be clinically relevant, with a power of 80%. Post-hoc analysis revealed a power of 96% to find a difference of 0.8 in LLSIRs. Nevertheless, we cannot completely rule out that minor changes could have been detected in a much larger sample. Furthermore, we do not rule out that with the emergence of magnetic resonance systems with field strengths of 3 Tesla and above, fetal lung development might soon be studied with such unprecedented accuracy that visualizing the effects of maternal smoking on the fetal lung *in vivo* will become possible. Nonetheless, effects have been reported for prenatal and/or postnatal exposure. Although our data might implicate a stronger role for postnatal exposure, uncertainties about the relative importance of smoking at different periods in a child's life remain and further studies are needed.

Our study has several limitations. First of all, we only evaluated LLSIRs on T2-weighted images. Therefore, we cannot completely rule out that by using diffusion weighted imaging or other sequencing protocols might unveil structural changes that we were not able to visualize using T-2 weighted images. However, as discussed previously measurement of LSSIRs on T2-weighted images successfully revealed structural and biochemical changes of the fetal lung in other studies. Furthermore, limitations include the retrospective design and the fact that we evaluated a group of high-risk pregnancies referred to a tertiary center. Information on smoking status and number of cigarettes per day was taken from patient's files. Additional information on the timing, duration, and degree of exposure during pregnancy was not available. Also, the mean number of cigarettes for mothers that reported smoking during pregnancy is low. Nonetheless, excluding women that reported smoking of less than ten cigarettes per day ($n=4$) did not impact our results (data not shown). To exclude possible confounding factors that have shown to lead to altered fetal lung development irrespective of maternal smoking status,[23] pregnancies with abnormal fetal growth, conditions where there is intrathoracic or extrathoracic compression of the fetal lung because of malformations or reduction in amniotic fluid, were excluded from the present investigation. In this sample of 100 women we found that 18% of mothers reported smoking during pregnancy. This figure is well in line with the 13% to 21% others have reported for Austria[24,25] suggesting a representative sample. Also, fetal characteristics such as crown–rump length and fetal gender were not significantly different between the two evaluated groups. Ideally our study would have a prospective setting, a better distribution of fetuses of mothers that reported smoking during pregnancy, and include only completely normal fetuses. However, such a study is unlikely because of the fact that MRI is still reserved for high-risk pregnancies because of its high cost and limited availability.

CONCLUSION

The present study showed no significant difference between fetal LLSIRs and fetal LLSIR progression over gestation of mothers that reported smoking during pregnancy compared with nonsmoking controls when evaluated by MRI using T2-weighted sequences. We propose further *in vivo* studies to investigate structural and functional changes to the developing lung to explain the detrimental effects of maternal smoking during pregnancy on respiratory health of neonates and infants.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Maternal smoking during pregnancy affects fetal lung development in utero, eventually leading to an impaired lung function and an increased risk of respiratory illness after birth.

WHAT DOES THIS STUDY ADD?

- Fetuses of mothers who reported smoking during pregnancy show similar lung signals lung signal progression over gestation on MRI as non-smoking controls.
- Possible structural or functional changes due to maternal smoking cannot readily be visualized by measuring fetal lung signals on TZ-weighted images.

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