Absence of harmful effects of magnetic resonance exposure at 1.5 T in utero during the third trimester of pregnancy: a follow-up study

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Abstract

In this study the possible adverse effects of in utero exposure to magnetic resonance (MR) conditions at 1.5 Tesla were examined. Thirty-five children between 1 and 3 years of age, and nine children between 8 and 9 years of age, that were exposed to MR during the third trimester of pregnancy, were checked for possible adverse effects in a follow-up study. Data on pregnancy and birth, the results of a neurological examination at 3 months, their medical documentary with emphasis on eye and ear functioning, and a questionnaire answered by their mothers were collected and evaluated. In five children abnormal test results were observed, that had no relation to the MR exposure. No harmful effects of prenatal MR exposure in the third trimester of pregnancy were detected in this study. © 2004 Elsevier Inc. All rights reserved.

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1. Introduction

Examination techniques based on the principles of magnetic resonance (MR) have the potential to become important diagnostic tools during pregnancy because of their noninvasive and nonionizing character. MR imaging (MRI) provides additional anatomical information to assess congenital anomalies of the fetus [1] and the placenta [2] in cases where sonography is not conclusive. Besides, MRI has several advantages in overcoming the difficulties that complicate prenatal ultrasound, such as maternal obesity and oligohydramnios. Also for maternal health problems during pregnancy, MRI seems to be the most suitable examination technique [3]. It is stated in the Policies, Guidelines, and Recommendations for MR Imaging Safety and Patient Management issued by the Safety Committee of the Society for Magnetic Resonance Imaging in 1991 that “MRI may be used in pregnant women if other nonionizing forms of diagnostic imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.” MR spectroscopy supplies biochemical information that might be helpful to diagnose inborn errors of metabolism and to determine changes in metabolism, e.g., due to hypoxia [4,5]. Furthermore, functional MRI might be a powerful tool to investigate normal and pathological brain development [6].

Although MR does not involve exposure to ionizing radiation, its potential health risks deserve further study. MR uses three different kinds of electromagnetic fields: static, time varying, and radio frequent electromagnetic fields. Theoretically, potential adverse effects on the fetus of all these three fields, both individually and combined, are possible. Several safety studies on MR exposure have been conducted. A small number of studies in human fetuses using regular MR imaging protocols within the safety recommendations that were performed in the late gestation period have not revealed any harmful effects on the fetus [7–9]. Also, exposure to static magnetic fields up to 4.7 Tesla in early gestation seems to induce no risk increase for adverse reproductive outcomes [10]. In addition, in vitro studies on proliferating human cells showed no adverse effects of static and time-varying magnetic fields [11]. However, animal studies on the safety of fetal MR are not conclusive and sometimes conflicting. In experimental procedures, hazardous effects to the fetus of long-duration exposure to static magnetic fields [12], of repetitive [13] or prolonged exposure [14,15] to all three magnetic fields, and of in utero exposure to a field of 4.7 Tesla [16] have been demonstrated. However, some of these studies were exper-
mentally deficient from both the MR exposure standpoint and the design of the experiments. The areas of concern are a reduced intrauterine growth [14–16] and harmful effects on temperature-sensitive tissue, e.g., eye lens [17] and testes [16]. Besides, very little is known about the possible damaging effects of the exposure to the very loud noise produced by common MRI and $T_2$-weighted fast imaging techniques, e.g., echo planar imaging and half-Fourier acquisition single shot turbo spin-echo (HASTE).

In order to determine the safety of MR techniques during pregnancy, more data on follow-up studies need to be presented. The aim of this study was to evaluate possible harmful effects of MR exposure on the fetus to a strong magnetic field. A prospective follow-up was performed in a group of normal fetuses that underwent an MR examination during the third trimester of pregnancy. Complementary to a general follow-up, special notice was given to the areas of concern, as observed in animal studies, and to hearing.

### 2. Material and methods

#### 2.1. Subjects

Between October 1998 and November 2000, 35 normal singleton pregnancies were included in the study “proton magnetic resonance spectroscopy of the human fetal brain” [18]. The gestational ages at the MR examination ranged from 30 to 41 weeks. All fetuses had an adequate growth for gestational age, a normal blood flow velocity in the umbilical artery as measured with pulsed wave Doppler, a normal fetal heart rate pattern, and showed no structural abnormalities on ultrasound examination. In addition, a group of nine children, who were previously examined with MR in utero in 1993 and 1994 in a previous pilot study [19], were included in this study for long-term follow-up. Between 1995 and 1997 no fetal MR examinations were performed in our medical center. All the pregnant women had provided written informed consent. The institutional review board had approved the study.

#### 2.2. MR exposure parameters

The MR procedures were conducted in a 1.5-Tesla clinical MR scanner (Magnetom, Siemens, Erlangen, Germany). MRI was performed using scout images (flip angle $30^\circ$, repetition time [TR] 15 ms, echo time [TE] 6 ms), and a HASTE sequence (TR 15 ms, 21 slices, acquisition band width 650 Hz/pixel). Two or three MR spectroscopy sequences were applied; a stimulated echo acquisition mode (STEAM) sequence at TE of 20 ms, and a point resolved spectroscopy (PRESS) sequence at a TE of 135 or 270 ms. The TR was 2500 ms. The number of acquisitions per spectrum was 256. Finally, the HASTE images were repeated at exactly the same localization to check for fetal movement. The total examination took 45 to 70 min. The radio frequency, field gradient, and static magnetic field exposure were within the Food and Drug Administrations’ safety guidelines. The experimental procedure was described in detail elsewhere [18].

### 2.3. Follow-up

Data on pregnancy, birth, a neurological examination at 3 months, eye and ear functioning at the age of 14 months, and the general health at the current age were collected. Information on pregnancy and birth was obtained by screening the medical status and a questionnaire sent to the mothers. In case of nonresponse a reminder was sent after 1 month. Special interest was paid to the health of the mother, including hypertension, diabetes, and infections. Also, smoking during pregnancy was noted. The neonatal data were checked for sex, birth weight, gestational age at birth, type of delivery, and arterial pH at birth.

At 3 months postnatal age, corrected for gestational age at birth, a neurological evaluation was performed in the short-term follow-up group by the assessment of general movements. This technique is considered a good predictor for long-term neurological outcome [20]. This information was not available for the fetuses that were exposed to MRI in 1993 or 1994.

After written permission of the mothers, a request for the medical documentation on the included children was sent to the infant health care centers. In the Netherlands all children are regularly screened at the ages of 3, 6, 9, 14, 24, and 36 months in an infant health care center. The general health was assessed, including growth curves for length, weight, and head circumference. Gross and fine motor functioning, social development, and communication were documented. Data on functioning of eyes and ears were noted. Any lacking information, as well as the health of the children at the time of this follow-up, were obtained from the questionnaire.

### 3. Results

In the short-term follow-up group, 30 of the 35 women responded after the initial letter. Three more answered after a reminder. In the long-term follow-up group, eight of nine women responded. All 41 answered the questionnaire and gave permission to ask for the medical information on the child at the infant health care center. The characteristics of the study group are detailed in Table 1.

During pregnancy, six of the included women smoked. From the MR examination onwards, three women developed hypertension, of which two as a feature of preeclampsia. Diabetes of pregnancy appeared in one case. Infections during pregnancy were not reported.

The average gestational age at birth was 39.2 weeks. Four children (10%) were preterm delivered between 34.5 and 36 weeks. The mean interval between MR examination and birth was 4 weeks. The average birth weight was 3382
grams, which is between the 50th and 75th percentile for gestation in the Dutch population. The average pH at birth was 7.26 (range 7.14–7.44).

The assessment of general movements at 3 months of age, only performed in the short-term follow-up group, was found to be normal in 32 children. In only one child a mildly abnormal movement pattern was observed. This test result correlates in almost 50% with the appearance of minor neurological dysfunction, and in slightly more than half of the cases with a normal neurological outcome [20]. The child is now 3 years old and has developed normally in gross and fine motor functioning as well as in communication.

The medical reports on the examinations at the infant health care centers showed good health in all 41 children. Thirty children developed normally along their individual health care centers showed good health in all 41 children. In personal contact by telephone with their mothers, no specific problems were mentioned.

Structure of the study group in mean values in our hospital in the period from 1997 to 2000

<table>
<thead>
<tr>
<th>Study Group</th>
<th>n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.5 ± 4.9</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>28.2 (53.8)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>15.4</td>
</tr>
<tr>
<td>Diastolic blood pressure &gt; 90 mm Hg (%)</td>
<td>7.7</td>
</tr>
<tr>
<td>Fetal/neonatal</td>
<td></td>
</tr>
<tr>
<td>Gestation at MR examination (weeks)</td>
<td>36 ± 2.7</td>
</tr>
<tr>
<td>Gestation at delivery (weeks)</td>
<td>39.2 ± 2.0</td>
</tr>
<tr>
<td>Preterm delivery &lt; 37 weeks (%)</td>
<td>10.3 (16.5)</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>3382 ± 632</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>8.4 ± 1.4</td>
</tr>
<tr>
<td>Apgar score at 5 mins</td>
<td>9.5 ± 1.0</td>
</tr>
<tr>
<td>Delivery</td>
<td></td>
</tr>
<tr>
<td>Spontaneous (%)</td>
<td>74.4 (61.8)</td>
</tr>
<tr>
<td>Primary cesarian section (%)</td>
<td>18.0 (14.1)</td>
</tr>
<tr>
<td>Secondary cesarian section (%)</td>
<td>2.6 (10.2)</td>
</tr>
<tr>
<td>Ventouse or forceps (%)</td>
<td>5.1 (13.9)</td>
</tr>
</tbody>
</table>

4. Discussion

No abnormalities were observed in 37 of the 41 children included in this study. In one child insufficient eye functioning, and in another invalid hearing was found, but in both cases the cause of these deficits was considered to be unrelated to the MR exposure. In two children abnormalities were reported that are discussed below.

Impaired articulation was diagnosed in one child at the age of 2½ years. Motor development was found to be normal in this child. Considering the progress made by increased practicing for 4 months since then, a persisting disability seems unlikely.

A second child was found to be abnormal for having a rigid walking pattern and being behind in speech at the age of 2 years. Flat feet and extreme knock-kneed legs were diagnosed. No reason was found for his speech problems. Since the diagnosis, both motor development and communication are progressing very well, but are still judged to be slightly behind at the age of 32 months. Although the anomalies in the boy’s legs are considered the reason for his abnormal walking pattern, the combination with his inexplicable problems in speech deserves a search for possible explanations. The birth weight of the child at a gestational age of 38.4 weeks was 2745 grams (P10 for Dutch population). The Apgar scores after 1 and 5 min were 8 and 10, respectively, with an umbilical cord blood pH of 7.26 and base excess of –10.5 mmol/l. Birth data, Apgar scores and umbilical cord pH showed no indications for the observed disabilities. However, ultrasonographic biometrics performed during pregnancy revealed a diminishing intrauterine growth from 33 weeks of gestation onwards. In the last week of pregnancy maternal hypertension developed. Due to an obstetric history of severe preeclampsia, parturition was induced. In the first weeks postpartum a catch-up growth was observed. In an ongoing pregnancy, intrauterine growth restriction probably would have been diagnosed. In addition to perinatal morbidity, growth-restricted neonates have an increased risk of developing cerebral palsy, mental handicaps, and learning difficulties [21]. Whether this is in fact the cause for the boy’s retardation is not clear. The decline in growth during pregnancy seems not to be related to the MR examination, performed at a gestational age of 37.6 weeks, because the growth restriction started long before that time.

No abnormalities in the hearing function as a result of MR exposure were observed. It is commonly known that the fetus responds to sound. By increasing the sound intensity the fetal response increases [22]. However, it has been demonstrated that high intense sound levels do not produce any effect on fetal cardiac activity, not even by MRI using T2-weighted imaging sequences, e.g., HASTE [23]. Most likely, the reduction of the sound intensity of 30 to 50 dB by the amniotic fluid and the fluid in the middle ear [24] diminishes the noise exposure to an acceptable level.

The study group contained a high percentage of women with a complicated obstetric history of prenatal death or
perinatal hypoxia. Their willingness to participate in the mentioned research project, that tries to obtain more information on the fetal neurological status, might have overruled the uncertainty caused by the lack of information on the safety of MR exposure during pregnancy. Therefore, a high rate of multiparity with its attendant beneficial effect on delivery was observed. Besides, a low average percentage of prematurity was observed, but some of the investigated fetuses were included at term.

It is not possible to judge if there are any potential adverse effects of MR exposure on reproductive functioning because of the young age of the examined children. This remains a matter of concern, because it has been shown in fetal mice that MR exposure in the period of gonad differentiation can cause a reduction of the daily sperm production, although in this study the MR exposure was during 8 h to a high field of 4.7 Tesla [16]. This reduction of the daily sperm production is supposed to be permanent, because Sertoli cells are critical for normal testis development and functioning [25]. Possible hazardous effects of MR examinations on reproduction, especially in early gestation, should therefore be investigated in future studies.

Although the effects of MR exposure in the prenatal period have not been fully determined yet, a trend towards the use of MR techniques at higher magnetic field strengths and with faster imaging sequences is observed. In the near future, more studies need to be performed to address the question of whether fetal MR examination is safe. Besides, long-term effects of MR exposure in the prenatal period need to be evaluated in follow-up studies.

5. Conclusion

By keeping the Specific Absorption Rate limits within the Food and Drug Administrations’ safety guidelines no harmful effects of prenatal MR exposure in the third trimester of pregnancy were detected in this study.

Acknowledgments

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References