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Abstract

Objective: To investigate whether steroids that induce lung maturation have acute effects on higher cortical function in the human fetus. **Methods:** Cortical auditory-evoked responses (CAERs) were recorded from 10 singleton fetuses between 29 and 34 gestational weeks by fetal magnetoencephalography (fMEG) using transabdominal auditory stimulation prior to and within 3 hours after administering 2×12 mg of betamethasone, at an interval of 18 and 24 hours. **Results:** The components of the CAER complex were categorized according to their latency: P2pm (186 + 20 ms, 90%), N2pm (260 + 34 ms, 50%), P3pm (474 + 36, 50%). In almost all of these cases the peak latencies of the fetal P2pm ($P = .042$) and P3pm ($P = .043$) were delayed after exposure to betamethasone (Wilcoxon rank test). The trend was also observable in N2pm ($P = .08$). **Conclusion:** Administration of betamethasone to expectant mothers was associated with acute change in higher cortical functions in the exposed fetuses. Implications regarding functional brain development need further evaluation.

Keywords

preterm labor, steroid administration, cortical auditory-evoked response, fetal magnetoencephalography

Introduction

Synthetic steroids have been used to accelerate premature lung maturation in fetuses threatened with preterm delivery for more than 30 years.^{1,2} The rate of preterm deliveries is approximately 11% to 14% in the United States and constitutes a major health issue.³ Prenatal steroid exposure prior to the completion of 34 weeks of gestation leads to a significant reduction in the occurrence and severity of respiratory distress syndrome in those preterm neonates, a decrease in the incidence and severity of intracerebral hemorrhage, ventriculomalacia and periventricular leucomalacia, and hence reduces neonatal morbidity and mortality associated with extreme and early preterm delivery.⁴⁻⁹

The prediction of imminent preterm delivery remains difficult. Depending on the methods of triage, a considerable number of women and fetuses have to be considered overtreated and do not profit from steroid exposure.¹⁰

The in utero exposure to synthetic steroids has been shown to trigger undesired effects in common monitoring parameters of the fetus such as heart rate patterns, heart rate variation, and gross body movements.¹¹⁻¹⁴ These changes may be due to steroid effects on the brain stem. They could be observed from about 24 hours after injection and were of transient character. Interestingly, the behavioral effects were more pronounced in

fetuses between 29 and 34 weeks than those earlier in gestation.¹³

Relevant to these observations in human fetuses, there have been a variety of reports from experimental studies using different animal models, which suggest that there might be both transient and even permanent effects of intrauterine steroid exposure onto functional forebrain development.¹⁵⁻²² Schwab et al have shown decreased complexity in the spontaneous electroencephalograph (EEG) activity in instrumented fetal sheep within 24 hours after betamethasone administration.²² These

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changes in EEG activity were accompanied by transient alterations in the neuronal cytoskeleton and synaptophysin, a synaptic marker protein,²³ and a decrease in cerebral blood flow by about 40%.²⁴

Fetal magnetoencephalography (fMEG) is a noninvasive method to examine human fetal brain function.²³⁻²⁸ It has in the past delivered best results when using auditory stimuli to analyze the long latency cortical auditory-evoked response (CAER) complex. It has been shown that the viability of this method begins from about 28 weeks of gestation.^{27,28} The CAERs reflect cerebral information processing rather than spread of excitation.^{29,30} The sound pressure levels in the frequency range used in these studies (500-1000 Hz) are attenuated by 30 to 40 dB by traversing through the layers of the abdominal and uterine walls, producing an intrauterine sound of 60 dB, which can be considered safe for the developing auditory organ.²⁸

Although steroid effects on the biophysical profile of human fetuses suggest changes in brain stem function and changes in the EEG of fetal sheep are indicative of effects on higher brain function, it is unclear whether antenatal steroid administration affects cortical function in human fetuses. We hypothesize that fMEG as a window to directly observe cortical processing in the human fetus will reveal steroidal effects on higher brain function during the time span when brain stem effects have been reported.

Methods

Participants

The study design was approved by the ethics commission of the Medical Faculty of the Friedrich Schiller University Jena. All participants were inpatients of the Department of Obstetrics at the University Hospital of the Friedrich Schiller University Jena, Germany. The participants were consecutively selected from the inpatient collective, according to the inclusion and exclusion criteria stated below. All participants chose to participate after the study protocol had been discussed and written informed consent was obtained. The patients were under continuous medical observation.

The patients received a course of 2×12 mg of betamethasone at an interval of 18 to 24 hours to accelerate fetal lung maturation on medical grounds (shortened cervical length of <30 mm \pm premature uterine contractions). Administration was strictly independent of participation in the study. In all but 1 case (patient # 4), the recordings were taken between 2 and 4 PM. The administration of the first dose immediately followed the return of the patients to the unit, and the second injection was timed between 11 and 12 AM the next day. In no case did the time between the second injection and the study recording exceeded 3 hours.

Inclusion criteria were maternal well-being, age >18 years, antenatal steroid administration for medical reasons, and written informed consent. To be studied, the women had to be transferred from the Department of Obstetrics to the



Figure 1. Experimental setting inside the magnetically shielded room with the sound applicator and Dewar in position. The recording system consists of 31 helium-cooled superconducting quantum interference devices (SQUIDs) fed by the corresponding number of symmetrical first-order gradiometers (coil diameter of 20 mm; baseline of 70 mm) arranged in an array of 145 mm in diameter. The system noise is below $10 \text{ fT Hz}^{-1/2}$ above 1 Hz.

biomagnetic facility. Therefore, high-risk conditions such as premature rupture of the membranes, progressive dilatation of the cervix, or persistent rhythmic uterine contractions during the time of triage led to exclusion from the study. In addition, sonographic signs of cerebral abnormalities, intrauterine growth restriction, preeclampsia, multiples, and preexisting chronic maternal disease were defined as exclusion criteria.

Data Acquisition and Analysis

All measurements were performed in the magnetically shielded room (AK 3b, Vakuumschmelze Hanau) of the Biomagnetic Center Jena with a 31-channel superconducting quantum interference device (SQUID) biomagnetometer (Philips, Hamburg, Germany; Figure 1). The recordings are an entirely safe and passive procedure. The only energy delivered to the fetus is auditory stimuli of physiological intensity (sound pressure level comparable to maternal voice in utero).²⁸

The experimental setting, data acquisition, and processing are described extensively by Schneider et al 2001.²⁶ In brief, each participant participated in 2 recording sessions of similar design: one prior to the first betamethasone administration, and a second within 3 hours after the second administration. Ultrasound was used to determine fetal position, to localize the fetal head, and to position the biomagnetometer (Figure 1). Each session consisted of 2 separate continuously recorded segments of 250 seconds (sampling rate 1000 Hz, band-pass filters 0.3 to 500 Hz). During these 2 segments, auditory stimuli of 500 Hz

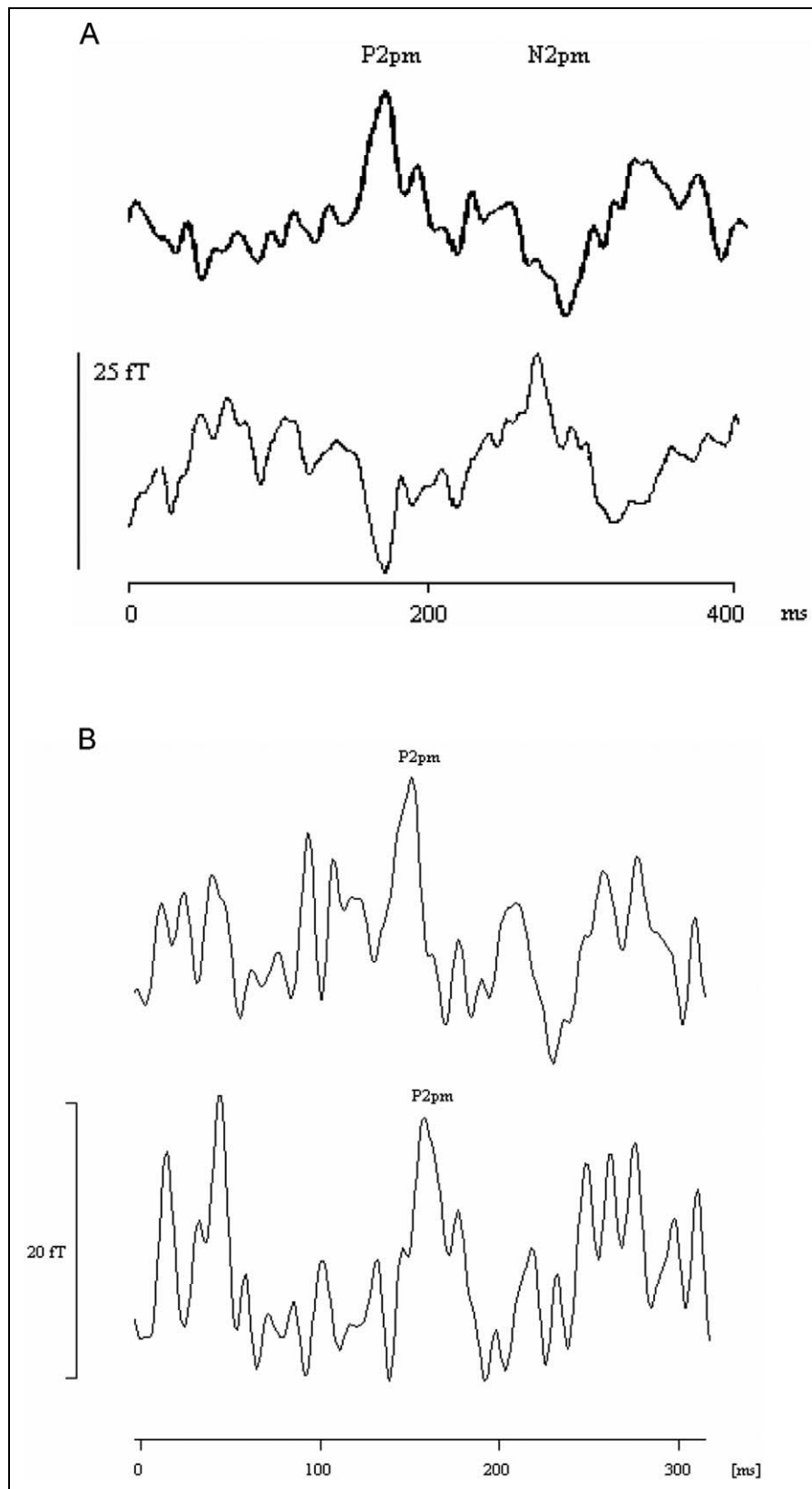


Figure 2. Examples of fetal cortical auditory evoked responses (CAERs). A, P2pm and N2pm components in 2 channels from the same recording with inverse polarity. B, Single channel plot of P2pm prior to (upper trace) and 3 hours after (lower trace) the second injection of betamethasone (patient 6 peak latencies P2pm 150 vs 172 ms). Note: no further components are in the same channels specifically for this fetus. Note: P for surface positive waves and N for surface negative waves (Rotteveel et al.)

Table 1. Pregnancy-Related and Perinatal Outcome Data^a

Patient Number	Age (years)	G/P	Tocolysis	GA (weeks)	EFW (g)	GAD (weeks)	BW (g)	Gender (M/F)	APGAR 5
1	27	1/0	Fenoterol	32	1925	35	2400	F	7
2*	28	1/0	Fenoterol	31	2033	39	2885	M	9
3	31	4/2	–	31	1830	40	4040	M	10
4*	21	1/0	–	34	2548	37	2510	F	9
5	30	2/0	Fenoterol	33	2236	39	3390	F	9
6	18	1/0	Fenoterol	32	1930	35	2949	M	9
7	36	2/1	NO	31	1860	39	3330	M	9
8	26	1/0	NO	29	1630	37	2990	F	10
9	20	1/0	–	30	1485	34	2180	M	9
10	29	1/0	–	31	2160	36	2550	M	8
11	23	1/0	–	31	1612	37	2630	M	9
12	31	1/0	–	30	1950	36	2630	F	9

Abbreviations: G/P, gravida/para, number of pregnancies including the current/number of previous deliveries; GA, gestational age at the time of investigation; EFW, estimated fetal weight; GAD, gestational age at the time of delivery; BW, birth weight; gender, gender of the newborn; APGAR 5, APGAR assessment at 5 minutes; NO, transdermal application of nitroglycerin.

^a Patients are consecutively numbered. Weeks of gestation are given as completed weeks. Patients 2 and 4 who had to be retrospectively excluded from the study indicated with an asterisk symbol.

tone frequency, 50 ms duration, a sound pressure level of 100 dB in air, and a variable interstimulus interval between 0.8 and 1.2 seconds were applied. The recordings were performed after an initial segment of quiescence and separated by another segment of quiescence of 250 seconds each. The auditory stimuli were delivered to the maternal abdomen from outside the magnetically shielded room via a 5-m plastic tube.

Data were preprocessed to remove (a) maternal and fetal cardiomagnetic activity and (b) random noise. (a) Maternal and, consecutively, fetal QRS complexes were averaged by performing template-based maximum coherence matching and these averages were subtracted from the raw data.^{28,31} This fetal beat-to-beat interval data were used to assess the ongoing level of fetal activity (see next paragraph) (b) The preprocessed data underwent triggered averaging after band-pass filtering and offset correction.²⁸

Signal verification was based on waveform comparison between the independent segments 1 and 2 of each session. If identical waveforms and peak latencies could be obtained from separate averaging of both segments, grand averages were calculated for latency determination.^{32,33}

As described previously, the components of the CAER complex were categorized according to their latency following the classification proposed in preterm neonates by Rotteveel et al.³⁴ In accordance to these findings, we designated the early components P1pm-N1pm and the late components P2pm-N2pm-P3pm (p for premature, m for magnetic; Figure 2).^{25,27,28} Following scientific convention, Rotteveel et al. used P for surface positive waves and N for surface negative waves in their EEG study performed in prematurely born infants.^{32,34}

Visual Assessment of Fetal Activity

During data processing, the time instants of the fetal QRS complexes are determined to achieve cardiac interference

reduction. This information was used to calculate and, retrospectively, display the fetal heart rate pattern (fHRP) during the recordings.³⁵ The fHRPs were classified by an obstetrician with routine experience in nonstress test assessment. Classification was based on specific visual criteria. Fetal quiescence was defined by a stable heart rate (variation of floating baseline of <10 bpm/3 min); oscillation bandwidth < ± 5 bpm; only isolated accelerations of >15 bpm/>15 seconds, and a floating baseline heart rate <160 bpm. These fHRPs were designated fHRP I. All fHRPs that did not fulfill these criteria were denominated fHRP II.³⁶

Results

A total of 10 participants underwent 20 successful sessions, allowing intraindividual comparison of component latencies. Table 1 summarizes the clinical characteristics. Of the initially recruited 12 women pregnant with singletons, the data of 2 had to be retrospectively excluded from analysis due to technical problems during the recording (patients # 2 and 4, see Table 1). Dosages of concurrent medication did not change between the consecutive sessions. One fetus was known to have a gastro-schisis (patient # 9). In 3 cases the mode of delivery was cesarean section. In all, 5 of the infants were female and 7 were male (Table 1). Within a single session, the fetal position did not change in any case. Ultrasound examination showed that maximum depth of the fetal head was 4.7 cm.

In each of the 20 separate sessions, at least 1 component of the fetal CAER could be detected. For the intraindividual comparison of latency before and after betamethasone administration, only those signals were used in which a component could be detected in both consecutive sessions. Five different components could be distinguished (mean latency + SD, percentage of detection): P1pm 76 + 9 ms, 20%; N1pm 109 + 9 ms, 20%; P2pm 186 + 20 ms, 90%; N2pm 260 + 34 ms, 50%; P3pm 474 + 36, 50%. Absolute

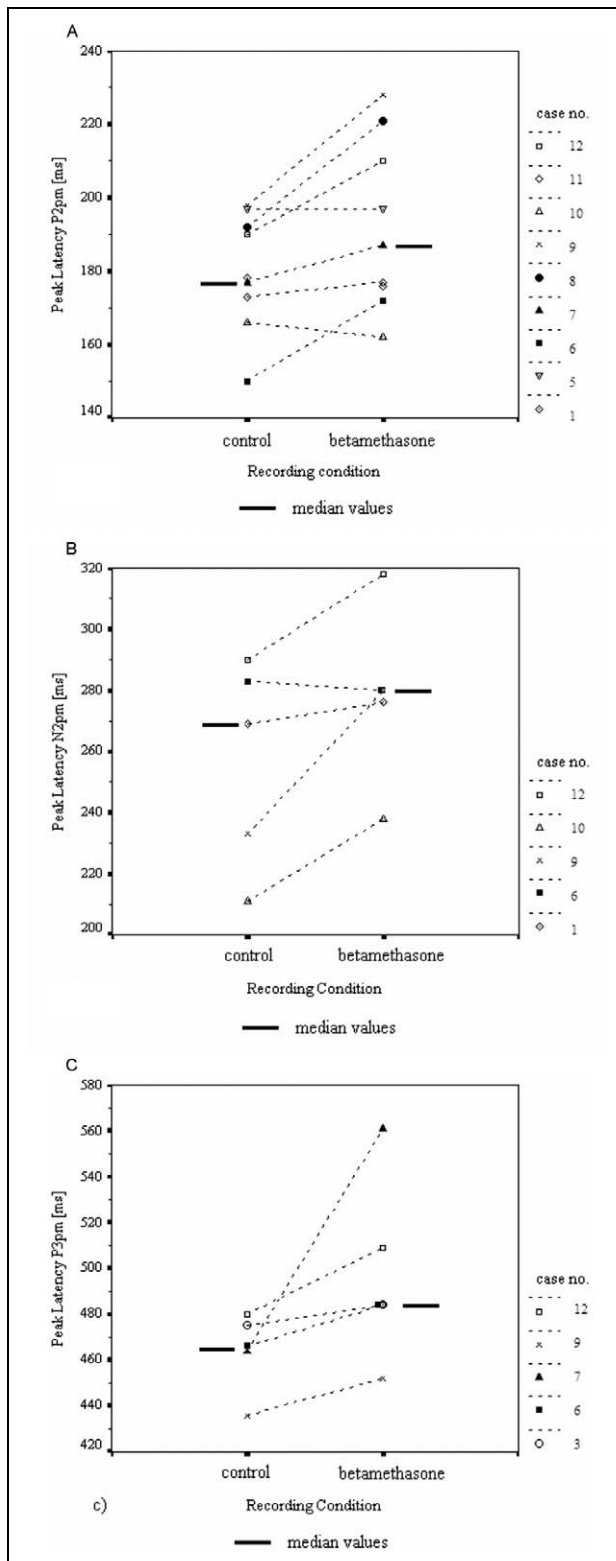


Figure 3. Individual peak latencies of the cortical auditory evoked response (CAER) components. Comparison of the peak latencies of (A) P2pm, (B) N2pm, and (C) P3pm between control (prior to betamethasone administration) and betamethasone (after betamethasone administration) conditions. Case number refers to those given in Table 1. The data from patients # 2 and 4 had to be excluded from further analysis due to technical defects of the recordings.

numbers of individual peak latencies of the fetuses are displayed in Figure 3A-C.

In a significant number of cases the occurrence of the fetal P2pm and P3pm components were delayed after exposure to betamethasone when compared to the control conditions (P2pm $P = .042$, median 178 vs 187 ms; P3pm $P = .043$, median 466 vs 484 ms; Wilcoxon rank test). The trend was also observable in the N2pm component not reaching the appropriate level of statistical significance ($P = .08$, median 269 vs 280 ms; Wilcoxon rank test).

The margin of latency delay from 180 ± 16 ms to 192 ± 23 ms (mean + SD) was statistically significant for the P2pm component ($P = .027$; paired student t test). Normal distribution was confirmed by Shapiro-Wilk testing. In contrast, owing to the small number of cases (only 5 cases each), the N2pm (from 257 ± 34 to 278 ± 28 ms, mean + SD, $P = .073$) and P3pm (from 464 ± 17 to 498 ± 41 , mean + SD, $P = .104$) components displayed a trend to delayed mean latencies after intrauterine betamethasone exposure.

When testing for possible confounders, we observed that the effect on P2pm was correlated with gestational age (Figure 4). Although P2pm in the control condition did not change significantly with age ($r^2 = -.36$; $P = .41$, Spearman), both the peak latencies after betamethasone exposure ($r^2 = -.61$; $P = .083$, Spearman) and the absolute intraindividual differences in peak latency ($r^2 = -.60$; $P = .068$, Spearman) displayed a trend toward a negative correlation with increasing gestational age (Figure 4). The 3 fetuses in the advanced gestational age were, in addition, exposed to fenoterol (Table 1). When excluding these fetuses post hoc from correlation analysis, the above described correlation factors became statistically significant (control condition, study condition, absolute difference P2pm: all $r^2 = -.83$; $P = .039$, Spearman).

Of the 10 fetuses, 7 presented with a fHRP II during both recording conditions. In 2 cases (case #s 7 and 9), the fetuses displayed fHRP II during control and fHRP I during the post exposition conditions. The fHRP of the remaining fetus (case 1) fulfilled the visual criteria of fetal quiescence during both recordings. In those rare cases where gestational ages and concurrent medications were comparable, the fHRP did not relate to any obvious systematic differences in the latencies of P2pm (ie, cases 1 vs 5; 9 vs 8 or 12; 7 vs 11; see Table 1 and Figure 3A).

Discussion

We examined the acute effects of betamethasone on the long latency components of the CAERs as markers for cerebral stimulus processing. After the intrauterine exposure to betamethasone at the dose used to accelerate fetal lung maturation, we observed a delayed cortical processing of the pure 500-Hz tone used as a stimulus here in almost all of the cases studied. To our knowledge, this is the first study demonstrating acute effects of antenatal steroid administration on higher brain function of the human fetus. The data are in agreement with the suspicion of acute steroid effects on cortical brain function, which has emerged from experimental studies.²²

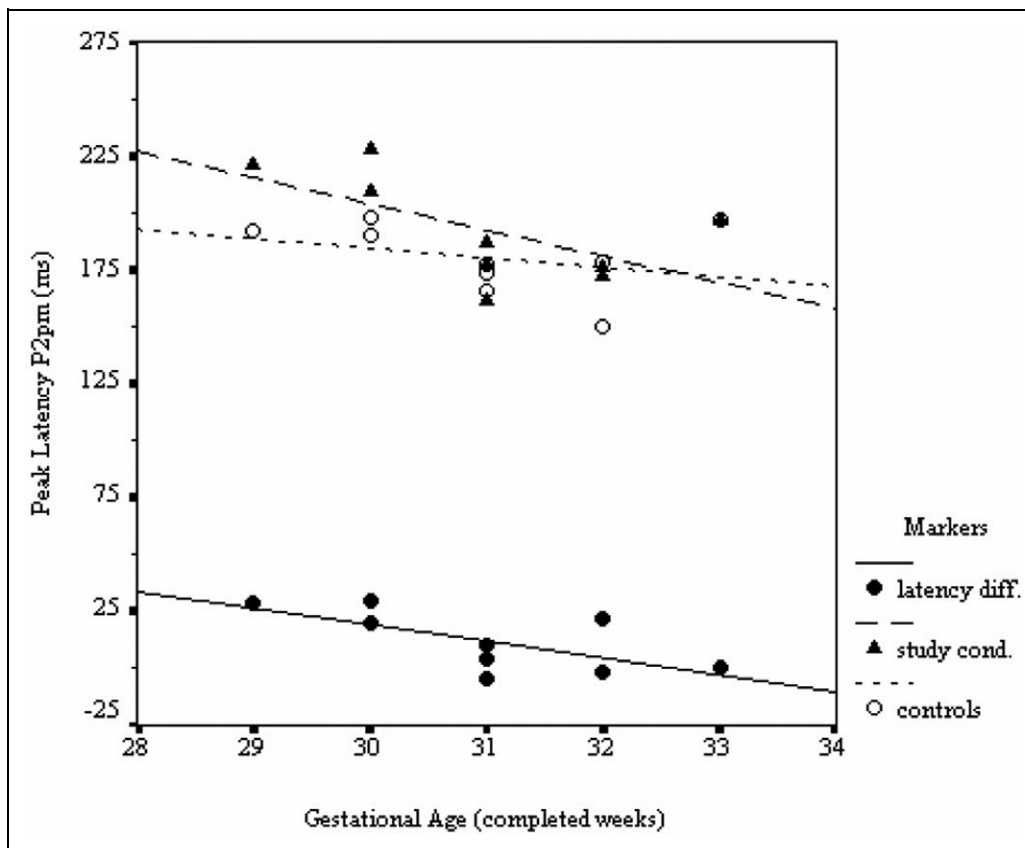


Figure 4. Latency relation with gestational age. Controls—P2pm peak latency prior to betamethasone exposure ($r^2 = -.36$; $P = .41$); study condition—P2pm peak latency after betamethasone exposure ($r^2 = -.61$; $P = .089$); latency difference—absolute intraindividual latency differences of P2pm ($r^2 = -.60$; $P = .068$). All correlations were calculated using Spearman correlation coefficient.

The previous studies examining the effects of prenatal steroid therapy onto evoked cerebral activity were performed after delivery and hence at variable times following betamethasone administration.³⁶⁻³⁸ de Zegher et al described a transient acceleration of the N1 component in somatosensory evoked potentials within the first week of life when betamethasone was combined with thyrotropin to induce prenatal acceleration of lung maturation.³⁶ In contrast to the current study the described effect most likely represents a maturational influence rather than an acute effect on fetal brain function. In 2 other studies neither the short latency auditory brain stem response nor the visually evoked cortical response were affected in premature newborns by antenatal steroid exposure.^{36,39} Amplitudes of CAER were shown to be influenced by steroid application in adults.^{39,40} They are generally small in fMEG and cannot be considered a dependent parameter because of the varying distance between sensors and source but may have an impact on overall detection.²⁸

That the cortical function of premature fetuses is primarily affected is in agreement with the data from Colberg et al, showing a more pronounced decrease in synaptic density to betamethasone exposure in fetal sheep at 0.7 gestation compared to fetal sheep at 0.83 gestation.⁴¹

Two types of steroid receptors have been described in the brain: mineralocorticoid or type I receptors are almost

exclusively distributed in the hippocampus. They show excitatory effects mediated by suppressing serotonergic hyperpolarization, leading to perpetuation of synaptic transmission. Glucocorticoid or type II receptors, which occur throughout the brain, tend to decrease neuronal excitability via interaction with the noradrenergic system.⁴²⁻⁴⁵ Synthetic steroids as such bind almost exclusively to type II receptors.^{44,46}

There are several possible confounders to our observations: All the recordings were performed in the early afternoon to control for diurnal changes, but we did not control for diet, beverage consumption, or other habits the participants might have had. The cerebral processing of auditory stimuli relates to the sleep state of the participant.⁴⁶ Acute cortisol administration is known to promote non-rapid eye movement (REM) sleep in human beings.⁴⁷ The peak latency of the CAER is known to increase during quiet sleep.³⁰ The pre-classification of fetal activity levels from a visual inspection of fHRP is not the current multimodal state-of-the-art method to assign the fetal behavioral state.⁴⁸ Ultrasound observation during fMCG recordings is not readily applicable because of its magnetic interference on the signal. With only minimal means to compare fetal activity level, such effects were not observed.

In our sample of 12 women, only 1 eventually delivered prior to the completion of 34 weeks of gestation, whereas 8 gave birth prematurely. These outcome parameters underline the

selection bias that had to be made according to the necessity of transportation off the limits of the obstetric unit. More recently the guidelines in our department were changed to a stricter handling of antenatal steroid administration to reduce the number of overtreated fetuses. Some of the participants in the described sample would under current policies not have been liable to receive steroid treatment. However, this stable sample represents patients with less choriodecidual inflammation, eliminating one of the potentially confounding factors. A confounding effect of the concurrent tocolytic medication with fenoterol cannot be ruled out.⁴⁹ The major limitation to our study is the small sample size that for the sake of controllable experimental conditions in these participants restricts the statistical power to nonparametrical testing and a narrow margin of statistical conviction. The fact that we observed a significant difference based on P2pm only may be just related to the fact that we were able to detect P2pm 90% of the time as opposed to other components which varied between 20% and 50%.

Antenatal steroid administration has been a life saving measure for thousands of preterm neonates worldwide since its introduction over 30 years ago. Long-term follow-up studies have not shown persistent negative effects, therefore, the benefits of treatment to date outweighs the potential risk.^{2,4}

However, this study indicated that betamethasone administration to the mother is associated with acute changes in higher cortical function in the exposed fetuses. The results suggest that a correlation might exist between the demonstrated effects and the gestational age at the time of the exposure. This study shows that it is mandatory for further in-depth investigation to determine whether there are such associations and whether these effects are transitory or permanent.

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Authors' Note

Uwe Schneider, MD, Matthias Schwab, MD, Jens Haueisen, PhD, Ekkehard Schleussner, MD, and Hans Joachim Seewald, MD, conceived the study hypothesis, study design, and experimental protocol. Christian Arnscheidt, MD, Uwe Schneider, MD, and Ekkehard Schleussner conducted the majority of the recordings. Uwe Schneider and Matthias Schwab acted as the major contributors to the writing of the manuscript. All the authors read, edited, and eventually approved the manuscript prior to submission. The Ethics Committee of the Medical Faculty at the Friedrich Schiller University of Jena, Germany, approved the study as described in the manuscript dated June 12, 2002 (Ref 0889-06/02).

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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