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The influence of betamethasone on fetal heart rate variability, obtained by non-invasive fetal electrocardiogram recordings☆

Kim M.J. Verdurmen[a,*], Guy J.J. Warmerdam[b], Carlijn Lempersz[a], Alexandra D.J. Hulsenboom[a], Joris Renckens[a], Jeanne P. Dieleman[c], Rik Vullings[b], Judith O.E.H. van Laar[a], S. Guid Oei[a,b]

[a] Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven, The Netherlands
[b] Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
[c] MMC Academy, Máxima Medical Centre, Veldhoven, The Netherlands

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ABSTRACT

Background: Betamethasone is widely used to enhance fetal lung maturation in case of threatened preterm labour. Fetal heart rate variability is one of the most important parameters to assess in fetal monitoring, since it is a reliable indicator for fetal distress.
Aim: To describe the effect of betamethasone on fetal heart rate variability, by applying spectral analysis on non-invasive fetal electrocardiogram recordings.
Study design: Prospective cohort study.
Subjects: Patients that require betamethasone, with a gestational age from 24 weeks onwards.
Outcome measures: Fetal heart rate variability parameters on day 1, 2, and 3 after betamethasone administration are compared to a reference measurement.
Results: Following 68 inclusions, 12 patients remained with complete series of measurements and sufficient data quality. During day 1, an increase in absolute fetal heart rate variability values was seen. During day 2, a decrease in these values was seen. All trends indicate to return to pre-medication values on day 3. Normalised high- and low-frequency power show little changes during the study period.
Conclusions: The changes in fetal heart rate variability following betamethasone administration show the same pattern when calculated by spectral analysis of the fetal electrocardiogram, as when calculated by cardiotocography. Since normalised spectral values show little changes, the influence of autonomic modulation seems minor.

1. Introduction

Cardiotocography (CTG) is used for fetal monitoring worldwide. One of the most important parameters to assess in CTG monitoring is fetal heart rate variability (HRV). Normal fetal HRV is a reliable indicator of fetal wellbeing, while decreased fetal HRV is associated with poor neonatal outcome (acidosis, low Apgar score and death) [1]. The fetal heart rate (HR), and thus HRV, is regulated by a complex interplay of the sympathetic and parasympathetic branches of the autonomic nervous system [2]. Spectral analysis (frequency analysis) of fetal HRV can be used to quantify these changes in autonomic regulation [3–8]. The low-frequency (LF)-component reflects baroreceptor reflex activity, and is both sympathetically and parasympathetically mediated [9]. The high-frequency (HF)-component is associated with fetal respiration, and is solely parasympathetically mediated [9].

Antenatal betamethasone administration plays an important role in the clinical management of threatened preterm delivery between 24 and 34 weeks of gestation (wG). It enhances fetal lung maturation and results in a significant reduction in, amongst others, neonatal mortality and respiratory distress syndrome [10]. However, betamethasone can easily cross the placenta [11] and influence fetal autonomic modulation and thus fetal HRV. Since fetal HRV is an important marker for fetal distress, knowledge on the influence of betamethasone on autonomic regulation is needed to avoid misinterpretation of changes in fetal HRV following betamethasone administration, and therefore prevent unnecessary iatrogenic preterm delivery.

Results of previous studies describing the effect of betamethasone on fetal HRV indicate that fetal HRV increases during the first day, followed by a decrease during days 2–3 [12]. Values returned to baseline during day 4. However, these studies were performed using

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* Corresponding author at: Department of Obstetrics and Gynaecology, Máxima Medical Center, Veldhoven, P.O. Box 7777, 5500 MB Veldhoven, The Netherlands.
E-mail address: kimverdurmen@live.nl (K.M.J. Verdurmen).

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CTG and measured the fetal HR by Doppler-ultrasound. With CTG, the fetal HR is averaged over several heartbeats and therefore beat-to-beat information is lacking. As a consequence, it is not possible to perform reliable spectral analysis.

The aim of this study is to quantify the effects of maternally administered betamethasone on spectral values of fetal HRV. To perform a reliable calculation of LF-and HF-power, we extracted beat-to-beat fetal HR information from non-invasive abdominal fetal ECG recordings [13].

2. Material and methods

We performed a prospective, longitudinal cohort study at the Máxima Medical Centre, Veldhoven, the Netherlands. This is a tertiary care teaching hospital for obstetrics. The study protocol was approved by the Medical Ethical Committee of the Máxima Medical Centre. Participants were included after written informed consent.

2.1. Study population

As described in our study protocol, we aimed for at least 50 inclusions and expected to end with 10–20 complete sets of measurements due to the anticipated loss to follow-up in this study group. We were not able to perform a power calculation, since this is the first study describing a five-day follow-up period following betamethasone administration with non-invasive abdominal fetal ECG recordings. From March 2013 until July 2016, women with a singleton pregnancy, at risk for preterm delivery and admitted to the Obstetric High Care unit were asked to participate in this study. All women requiring betamethasone (Celestone Chrondose®, Schering AG, Berlin, Germany; 2 doses of 12 mg intramuscularly, 24 h apart) as part of standard clinical management were eligible to participate. In case of threatened preterm labour, co-administration of tocolytic drugs was allowed. Nifedipine was used to attenuate uterine contractions, occasionally complemented by indomethacin in case of continuous uterine contractions when betamethasone administration was not yet completed. In case of preterm prelabour rupture of membranes, patients also received antibiotics (erythromycin 250 mg 4 times daily during 10 days) as part of the standard treatment protocol. Women were excluded in case of maternal age < 18 years, multiple pregnancy, fetuses with a known congenital malformation, signs of intra-uterine infection or fetal growth restriction (defined as the estimated weight of the fetus below the 5th percentile for gestational age).

The following data was gathered prospectively: maternal gravidity and parity, indication for betamethasone administration, obstetrical and general medical history, gestational age at inclusion and administered medication during the study period. Follow-up measurements of study participants lasted from the date of informed consent until five days after the first measurement, discharge or delivery, whichever occurred first. Postpartum, neonatal charts were checked for any indications of congenital anomalies that might have influenced the measurements and for missed cases of growth restriction defined as birth weight below the 5th percentile (corrected for gestational age, parity and sex of the neonate).

2.2. Outcome measures

The outcome of interest was fetal HRV, which was quantified using both time-domain features (short-term variability [STV] and long-term variability [LTV]) and frequency- domain features (LF- and HF-power).

2.3. Measurements

We performed series of measurements as visualised in Fig. 1. Recordings were obtained while the patient was lying in a semi-recumbent position, to prevent supine hypotension syndrome. The duration of a measurement was approximately 30 min. The total measurement was divided in segments of 60 s, and per segment HRV parameters were calculated. The median value of all available segments was used for statistical analysis.

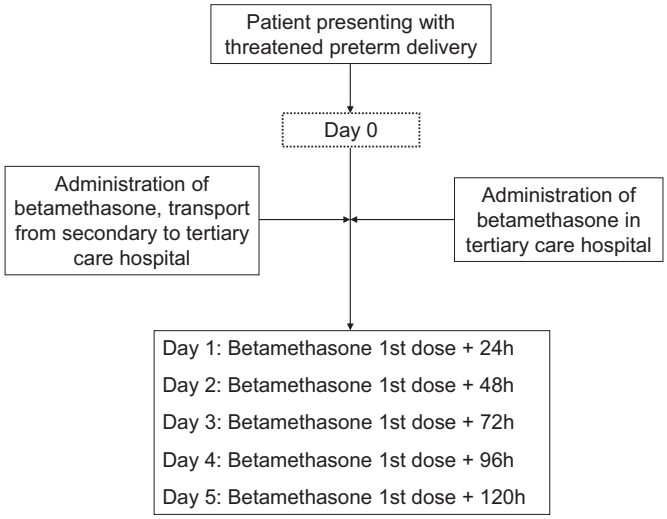

Fig. 1. Flowchart of patient inclusion and timing of measurements.

To reduce the influence of diurnal variations, the timing of measurements within a series was fixed for each patient (between 20 and 28 h after the previous measurement). In order to respect the patient's night rest, no measurements were performed between 24.00 h and 7.00 h.

Complete series were defined as series including a reference measurement, and measurements during at least days 1, 2, and 3. In case one or more of these measurements was missing, the patient was excluded.

2.4. Reference measurement

Most patients were transferred from secondary care hospitals in the region. Since for these patients betamethasone treatment was initiated prior to transport, they had no baseline measurement (0-measurement, on day 0). Former research showed that all changes in fetal HR and HRV returned to baseline values from day 4 onwards (96 h after the first dose of betamethasone) [12]. Therefore, we included transferred patients if we were able to conduct a measurement during day 4 or 5 following the first dose of betamethasone. We used the median value of the measurements during day 0, and/or day 4, and/or day 5 as the “reference measurement”. By means of a full range plot, we verified whether our reference measurement was comparable with the real 0-measurement in a separate subset of patients. Included cases with good quality measurements on day 0, and day 4, and/or day 5 were selected.

2.5. Data acquisition and signal processing

The fetal ECG was recorded on six channels, using a fixed configuration on the maternal abdomen as illustrated in Fig. 2. The abdominal signals were recorded by two non-invasive electrophysiological monitoring devices; the Nemo fetal monitor (Nemo Healthcare BV, Eindhoven, the Netherlands) and the Porti system (TMSi, Enschede, the Netherlands), operating at sampling rates of 500 Hz and 512 Hz, respectively. Both devices were approved by the Medical Technical Service Department of the Máxima Medical Centre.

The recordings were analysed offline. Recordings were first preprocessed to suppress the maternal ECG using a dynamic template subtraction technique [14]. The signals remaining after maternal ECG suppression were spatially combined to enhance the signal-to-noise