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

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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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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

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

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.

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 pre-processed 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

Fig. 2. The fetal electrocardiogram.

The six channel fetal electrocardiogram is recorded with electrodes on the maternal abdomen, placed in a fixed configuration. The ground (GND) and reference (REF) electrode are placed near the belly button. The electrodes are connected to a battery operated data acquisition system (Nemo Healthcare BV), which filters, amplifies, and digitises the data for further processing. This system is connected to a computer.

ratio of the fetal ECG with respect to remaining electrophysiological interferences (e.g. muscle activity) [15,16]. Finally, a wavelet-based R peak detection was performed to obtain a beat-to-beat fetal HR [17]. In case no R peaks were detected using all six channels, channels with good quality fetal ECG were selected manually to avoid negative effects on the spatial combination of those channels that were dominated by interferences.

Prior to HRV analysis, the obtained heart rates were automatically analysed for incorrect R-R intervals. R-R intervals shorter than 0.3 s or longer than 1.2 s (< 50 or > 200 bpm) were assumed to be incorrect

[17]. Furthermore, if an R-R interval deviated > 12% from a running average R-R interval, it was also assumed to be incorrect [18]. The incorrect R-R intervals were replaced by linear interpolation. To ensure reliable spectral analysis, only heart rate segments of 60 s were included with < 20% interpolation and less than 5 s of consecutive interpolation [18]. We only included measurements with at least three segments that met the quality criteria.

2.6. Heart rate variability analysis

Since spectral analysis requires signals that are equidistantly distributed in time, the obtained heart rates are resampled at 4 Hz by linear interpolation. Spectral analysis is performed using a continuous wavelet transform [19]. Based on previous studies, the following frequency bands were selected: total frequency 0.04–1.5 Hz, LF 0.04–0.15 Hz and HF 0.4–1.5 Hz [4,6,9,20,21]. LF- and HF-power was expressed in absolute units (ms^2) and normalised units ($\text{LFn} = \text{LF-power}/\text{total power}$, $\text{HFn} = \text{HF-power}/\text{total power}$).

In addition to spectral powers, STV and LTV were calculated to compare our results to prior research performed with CTG measurements. LTV was calculated as the difference between the maximum and minimum R-R interval in every 60 s segment [22,23]. STV was calculated as the mean of absolute differences between consecutive R-R intervals in every 60 s segment [23]. Note that in CTG (ultrasound) monitoring, STV is defined based on epochs (e.g. 1/16th of a minute) because fetal HR is not acquired beat-to-beat. However, since the gold standard for STV is beat-to-beat variation [22], we used the aforementioned ECG-based STV calculation.

2.7. Statistical analysis

Descriptive statistics were used to describe the study population and outcome measures. No statistical analysis was performed. For each fetus

Fig. 3. Overview of the inclusion process.

*Patients were excluded if the measurements were not performed within the time window (between 20 and 28 h after the previous measurement), had one or more missing measurement in the series, or were insufficient in data quality.

Table 1
Patient characteristics and pregnancy outcome.

Case	Maternal gravidity, parity	Indication	Relevant history	wG at inclusion	Medication during study period (other than betamethasone)	wG at delivery	Apgar Score 1'/5'	NICU admission
1	G1P0	TPL	–	24 + 4	Nifedipine, indomethacin, LMWH	25 + 4	7/8	Yes
2	G1P0	PE	May-Turner, thrombosis	33 + 4	LMWH, methyl dopa	34 + 3	9/10	No
3	G2P1	VBL	Gestational diabetes	31 + 1	Progesterone (vaginal), nifedipine, augmentin	33 + 5	9/10	No
4	G2P1	PPROM	–	33 + 0	Nifedipine, erythromycin	34 + 1	8/9	No
5	G2P1	TPL	–	26 + 2	Nifedipine	39 + 5	5/9	No
6	G1P0	TPL	LEEP	29 + 2	Nifedipine	40 + 1	9/10	No
7	G1P0	VBL	–	25 + 2	–	38 + 1	9/10	No
8	G2P1	TPL	Pre-existent hypertension	26 + 1	Nifedipine, labetalol, magnesium sulphate, indomethacin	36 + 6	8/10	No
9	G2P1	TPL	–	25 + 6	Nifedipine, progesterone (vaginal)	40 + 4	9/10	No
10	G2P1	VBL	–	33 + 0	Iron tablets	37 + 5	9/10	No
11	G1P0	TPL	–	30 + 6	Nifedipine	32 + 6	9/10	No
12	G1P0	VBL	LEEP	26 + 6	–	33 + 5	?/10	No

Birth weight percentile: percentiles are corrected for parity, gestational age at delivery and sex, and apply to the Dutch population. Source: Perined.

Abbreviations: LEEP = loop electrosurgical excision procedure of the cervix, LMWH = low molecular weight heparin, NICU = neonatal intensive care unit, PE = pre-eclampsia, PPRM = premature prelabour rupture of membranes, TPL = threatened preterm labour, VBL = vaginal blood loss, wG = weeks of gestation.

a different number of segments were available during the study period, mainly due to variations in ECG signal quality. The result on each day was compared to the reference measurement.

3. Results

Initially, 68 women were included in this study. The inclusion process is depicted in Fig. 3. Three patients requested withdrawal from the study because of poor prognosis for an extreme premature child (1), technical issues (1) and inconvenient timing of measurements for the patient (1). In one patient unexpected intra-uterine fetal death occurred during the study period. Extensive evaluation revealed no evident cause. In 28 patients we were able to obtain a complete set of measurements, of which 16 were excluded due to insufficient data quality (fewer than three good quality segments per measurement) in one or more of the measurements. Eventually, 12 patients with a complete set of sufficient data quality were included for analysis. Table 1 shows the patient characteristics of the 12 included cases.

3.1. Reference measurement

Measurements during day 0, and/or day 4, and/or day 5 were compared in five patients. In Fig. 4, absolute LF, HF, LFn and HFn are displayed. As expected, the absolute fetal HRV values showed some inter- and intra-patient variation, which can mainly be explained by variation in the segments that were recorded during active and quiet states and by variation in gestational age of the fetuses. LFn and HFn

show better comparability during day 0, 4, and 5, since these normalised values are not masked by changes in total power. For instance, these values are not influenced by fetal activity states.

3.2. Heart rate variability outcomes

Our outcome of interest was fetal HRV. Descriptively, in Fig. 5 we see an increase in LTV and STV on day 1, and a decrease on day 2 and 3 as compared to the reference measurement. For LF and HF, we see the same trend. For LFn and HFn we see little changes during the study period.

3.3. Segments available for analysis

The amount of segments that was available for analysis is displayed in Table 2.

4. Discussion

4.1. General discussion

Up to our knowledge, this is the first study to report on the influence of betamethasone on spectral estimates of fetal HRV measured by non-invasive fetal ECG recordings with electrodes on the maternal abdomen. As we anticipated, over 80% of our inclusions could not be used in the final analysis; we aimed for at least 50 inclusions and expected to end with 10–20 complete sets of measurements. This was mainly due to

Fig. 4. Verification of the reference measurement.

Median value and full range plot of low-frequency (LF)-power, high-frequency (HF)-power, normalised LF-power (LFn) and normalised HF-power (HFn) on days 0, and/or day 4, and/or day 5 for five patients.

Fig. 5. Changes in fetal heart rate variability parameters during the study period.

The x-axis shows the number of days after the first administration of betamethasone. Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5. The outcomes are depicted as median values with interquartile ranges.

Abbreviations: LF = low-frequency power, LFn = normalised low-frequency power, LTV = long-term variability, HF = high-frequency power, HFn = normalised high-frequency power, STV = short-term variability.

Table 2
Amount of segments available for analysis.

	Segments available for analysis/total recorded segments	Percentage of segments available for analysis
Reference measurement		
Day 0 ^a	103/110	94%
Day 4 ^b	201/305	66%
Day 5 ^c	162/278	58%
Day 1	332/580	57%
Day 2	214/403	53%
Day 3	223/407	55%

On the other study days, FHR segments were available in all 12 patients.

^a Day 0: FHR available in 3 out of 12 patients.

^b Day 4: FHR segments available in 10 out of 12 patients.

^c Day 5: FHR segments available in 8 out of 12 patients.

loss to follow-up and insufficient data quality. Insufficient data quality is a general problem encountered when studying HRV with spectral analysis [24,25]. We applied a high standard for good signal quality; only measurements containing at least three segments with good signal quality per measurement were selected. Since we preferred data quality over data quantity, only a limited number of series (12) were available eventually. Therefore, we decided to describe our study results and not perform any statistical analysis. Hence, our study results should be interpreted appropriate caution.

4.2. Heart rate variability outcomes

We found a similar trend in LTV and STV with fetal ECG analysis as compared to previous studies that used CTG analysis [12].

A more accurate way to evaluate autonomic modulation is spectral analysis of the beat-to-beat fetal HR. LF- and HF-power are absolute spectral estimates, that relate to LTV and STV. As expected, the same trends are seen during the study period for these parameters.

Due to normalisation, relative changes in LF- and HF-power are not masked by changes in total power. Both LFn and HFn show little changes during the study period. This indicates that the influence of

autonomic modulation following corticosteroid administration is minor, since there are no relative changes in LF- and HF-power objectified.

4.3. Segments available for analysis

As shown in Table 2, the mean available amount of segments per day was always > 50%. One has to bear in mind that this is in selected series with sufficient quality of the performed measurements. There are no obvious differences between the measurement days; the amount of available segments is steady between 52% and 57%. Only the measurements performed on day 0 show a higher percentage of available segments. However, only 3 out of 12 patients were eligible for a measurement during day 0.

4.4. Considerations

We defined the reference measurement as the median value of the measurements during day 0, and/or day 4, and/or day 5. Although relatively good comparability was seen for fetal HRV values, this remains second best with regard to a true baseline measurement.

The high number of measurements that had to be excluded due to poor signal quality, can mainly be explained by presence of vernix caseosa. This fatty layer surrounds the fetus and results in an electrical isolation, which diminishes the signal amplitude of the fetal ECG. Especially between 30 and 34 wG, this layer causes a poor signal-to-noise ratio [24,26]. We do not expect any other major influencing factors on signal quality. Analysis of the data was mainly performed computerised. It is possible that failed registration resulted in selection bias, although the influence is expected to be minor.

By including patients receiving other pregnancy-related drugs rather than betamethasone, we aimed to obtain information that is applicable in daily clinical practice. Nifedipine and indomethacin seem to have no clinically important effect on fetal HRV, while magnesium sulphate can cause decreased fetal HRV and cases of bradycardia have been described [27]. In one case, magnesium sulphate was administered during days 1, 2 and 3 of the study period. Since magnesium sulphate was not administered during the reference measurement, this might have had some influence on the study results. In one case

labetalol was administered to the patient; this was already started prior to the measurements and no changes in dosage occurred during the study period. Therefore, it is not likely that this had major influence on the study results. It is unlikely for amoxicillin-clavulanic acid, low-molecular weight heparin, methyldopa and progesterone to have any influence on fetal HRV parameters due to their mechanism of action.

Apart from pathological conditions, two major factors that one should consider when assessing fetal HR patterns are gestational age and fetal behavioural states [28]. Previous studies show that gestational age significantly affects the fetal HRV power spectrum, with a gradual increase in LF- and HF-power during gestation [24,29,30]. In this study, the included fetuses had a gestational age varying from 24 to 33 wG. Since we studied fetuses on successive days and were interested in relative changes in fetal HRV parameters, the influence of the increase in LF- and HF-power during gestation is likely to be minor. It is possible that an increase in time spent in the quiet state following betamethasone administration might be caused by disturbance of the maternal glucose metabolism [31], which is a known side effect of corticosteroids.

Fetal HRV and fetal movements are two parameters associated with fetal well-being. The reduction in both, due to betamethasone administration, can be misinterpreted as fetal deterioration and can therefore possibly lead to unnecessary iatrogenic preterm delivery [32,33]. Most likely, the reduction in fetal movements is a direct effect of corticosteroid administration, possibly by occupying the glucocorticosteroid receptor in the central nervous system, suppressing neuronal activity and therefore reducing physical activity in the fetus [12]. No other signs of fetal hypoxia, like decelerations or abnormalities in Doppler flow velocity waveforms, have occurred after corticosteroid administration [32–36]. In addition, Shenhav et al. [37] demonstrated that reduced fetal HRV was not related to the fetal acid-base balance at birth when delivery occurred < 48 h following betamethasone administration. This study confirms these results, since the influence of autonomic modulation was found to be minor (reflected as no evident changes in normalised spectral powers during the study period). However, in fetal monitoring it is important to be aware of the side-effects, such as reduced fetal HRV and fetal movements.

5. Conclusion

The changes in fetal HRV following betamethasone administration show the same pattern when calculated by spectral analysis of the fetal ECG, as when calculated by Doppler-ultrasound CTG. The influence of autonomic modulation following corticosteroid administration is minor, since there are no relative changes in LF- and HF-power objectified.

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Author contributions

KV collected fetal ECG recordings, was involved in the study design and interpretation of the data and wrote the paper. GW was involved in the study design, processed the fetal ECG recordings, was involved in interpretation of the data and wrote the paper. CL, AH and JR were

involved in collecting the fetal ECG recordings. JD was involved in the statistical analysis and interpretation of the data. RV was involved in the study design, processing of the fetal ECG recordings and interpretation of the data. JvL and GO were involved in the study design and interpretation of the data. All authors discussed the results and commented on the manuscript. All authors approved on the final version of the manuscript.

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