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Short Term Fetal Heart Rate Variation in Intrauterine Growth Restriction: development of reference values for a new computational algorithm

(Kurzzeitvariation der fetalen Herzfrequenz
in intrauteriner Wachstumsretardierung:
Erstellung von Normkurven für einen neuen
Berechnungsalgorithmus)

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To my father,
who made me the person I am today

ABSTRACT

Cardiotocography (CTG), the continuous and simultaneous recording of the fetal heart rate (FHR) and the maternal contractions, is a method widely used for the assessment of fetal well-being, predominantly in pregnancies with increased risk of complications.

The Oxford system, developed by Dawes and Redman and implemented in the Sonicaid Fetalcare monitor, provides a computerised analysis of the CTG (cCTG) by taking into consideration a number of numerical, computer based parameters, with Short Term Variation (STV), a measure of the micro fluctuations of the FHR, being one of the most significant ones, especially in the monitoring of fetuses with Intrauterine Growth Restriction (IUGR).

The Dawes-Redman algorithm calculates the STV by dividing each minute into 16 segments, each one being 3,75 seconds long and including 7-10 fetal heartbeats, or 6-9 pulse intervals (STV16). The average pulse interval in each section is calculated and the STV16 derives from the difference of the average pulse intervals between two sections. This calculated STV16 does not, however, equal the beat-to-beat variation of the FHR.

A series of important studies has demonstrated that, when monitoring fetuses with preterm IUGR, STV16 values under 3ms correlate positively with the development of metabolic acidemia and should prompt to delivery.

Theoretically, measurement of the pulse interval in much smaller time fractions, so that every heartbeat would be taken into consideration (instead of one every 7-10 heartbeats), would lead to a more accurate approximation of the beat-to-beat variation with significant advantages for the antenatal monitoring of the fetus.

The IntelliSpace Perinatal by Philips Medical, which measures the STV by dividing each minute into 240 segments (STV240), attempts to better approximate the beat-to-beat variation of the FHR.

An effort in our department to implement the existing cut-off values of the STV16 as reference values for the new STV240 algorithm has resulted in highly abnormal findings, with STV240 values significantly below the cut-off values of the STV16.

This observation led to the hypothesis, that the reference values for the STV240 should be different, and, more precisely, lower in comparison to the existing reference values for the STV16. This hypothesis was not only based on clinical observation. The discrepancy noted between the two different algorithms is also logically sound, as it is to be expected that the variation between two subsequent beats will be notably lower as the variation between 7-10 subsequent heartbeats.

We therefore conducted a single-center, non-interventional, prospective clinical study in order to develop clinically relevant reference values for the STV240 and to compare the reference values for the STV240 to the ones for the STV16. At the same time, we studied the effects of RDS prophylaxis on STV240 and STV16, in order to verify if the known transient effects of corticosteroids on the STV could also be detected with the new algorithm for the STV240.

A total of 228 CTG traces from 94 patients (86 singleton and 8 twin pregnancies) were registered and included in the final statistical analysis for the development of the reference values.

The values of the STV240 were significantly lower in comparison to the ones of the STV16. Moreover, not only the mean values but 95% of the values for the STV240 lay beneath the existent cut-off value for the STV16.

The STV240 has a relative strong, statistically significant correlation with the STV16 (r=0,646, p<0,001). A medium, although statistically significant correlation (r=0,373, p<0,001) between week of pregnancy and STV240 was documented, whereas the correlation between STV16 and week of pregnancy was negligible.

A transient increase of both the STV240 and STV16 was documented in the first 24h after the first intramuscular corticosteroid administration, when compared to the STV240 and STV16 without RDS prophylaxis or at least 72h after. This was followed by a transient decrease of both the STV240 and STV16 between 24h and 72h after the first intramuscular corticosteroid injection

Our results confirmed our hypothesis and allowed us to calculate the reference values for the STV240. Of paramount importance for every clinician using the new algorithm in her or his everyday practice, is to know that the normal values for the STV240 (not only the mean value but also the 95th percentile) lie beneath the, up until now, established cut-off value for the STV16. This stresses the fact that every clinician using cCTG should be, in advance, well aware of the algorithm implemented in his cCTG monitors. Otherwise, there is the threat of unnecessary iatrogenic premature deliveries, with all relevant risks.

DEUTSCHE ZUSAMMENFASSUNG

Cardiotocographie (CTG), die kontinuierliche und gleichzeitige Aufzeichnung der fetalen Herzfrequenz (FHF) und der mütterlichen Kontraktionen, ist eine Methode, die weithin für die Beurteilung des fetalen Wohlbefindens verwendet wird, vorwiegend bei Schwangerschaften mit erhöhtem Komplikationsrisiko.

Das von Dawes und Redman entwickelte Oxford-System, welches im Sonicaid Fetalcare Monitor implementiert ist, bietet eine computerisierte Analyse des CTG (cCTG) unter Berücksichtigung einer Reihe von numerischen, computerbasierten Parametern an. Kurzzeitvariation (KZV), eine Maßnahme der Mikrofluktuationen des FHF, ist einer der bedeutendsten computerbasierten Parameter, vor allem bei der Überwachung von Feten mit intrauteriner Wachstumsrestriktion (IUGR).

Der Dawes-Redman-Algorithmus berechnet die KZV, indem er jede Minute in 16 Segmente unterteilt, wobei jedes 3,75 Sekunden lang ist und 7-10 fetale Herzschläge oder 6-9 Pulsintervalle (KZV16) enthält. Das mittlere Pulsintervall in jedem Abschnitt wird berechnet und die KZV16 ergibt sich aus der Differenz der mittleren Pulsintervalle zwischen zwei Abschnitten. Diese berechnete KZV16 entspricht jedoch nicht der beat-to-beat-Variation der FHF.

Eine Reihe wichtiger Studien hat gezeigt, dass bei der Überwachung von Feten mit früher IUGR KZV-Werte unter 3ms positiv mit der Entwicklung einer metabolischen Azidämie korrelieren und zur Entbindung führen sollten.

Theoretisch würde die Messung des Pulsintervalls in viel kleineren Zeitabschnitten, so dass jeder Herzschlag berücksichtigt wäre (statt eines alle 7-10 Herzschläge), zu einer genaueren Annäherung der beat-to-beat-Variation der FHF führen, mit deutlichen Vorteilen für die antepartale Überwachung des Fetus.

Das IntelliSpace Perinatal von Philips Medical, das die KZV auswertet, indem es jede Minute in 240 Segmente teilt (KZV240), versucht die beat-to-beat Variation der FHF besser anzunähern.

Ein Versuch, in unserer Abteilung, die vorhandenen cut-off-Werte der KZV16 als Referenzwerte für den neuen KZV240-Algorithmus zu implementieren, hat zu sehr

auffälligen Befunden geführt, wobei die KZV240-Werte deutlich unter den cut-off-Werten der KZV16 lagen.

Diese Beobachtung führte zu der Hypothese, dass die Referenzwerte für die KZV240 im Vergleich zu den vorhandenen Referenzwerten für die KZV16 niedriger sein sollten. Diese Hypothese beruht nicht nur auf der klinischen Beobachtung. Die zwischen den beiden verschiedenen Algorithmen bemerkte Diskrepanz ist auch theoretisch zu erwarten, weil die Variation zwischen zwei nachfolgenden Herzschlägen deutlich geringer als die Variation zwischen 7-10 nachfolgenden Herzschlägen ist.

Wir haben daher in unserer Klinik eine nicht interventionelle, prospektive klinische Studie durchgeführt, um klinisch relevante Referenzwerte für die KZV240 zu entwickeln und diese mit denen für die KZV16 zu vergleichen. Gleichzeitig haben wir die Effekte der RDS-Prophylaxe auf KZV240 und KZV16 untersucht, um zu prüfen, ob die bekannten transienten Effekte von Kortikosteroiden auf der KZV auch mit dem neuen Algorithmus für die KZV240 nachgewiesen werden können.

Insgesamt wurden 228 CTGs von 94 Patientinnen (86 Einlings- und 8 Zwillings-Schwangerschaften) registriert und in die endgültige statistische Analyse zur Entwicklung der Referenzwerte einbezogen.

Die Werte der KZV240 waren im Vergleich zu der KZV16 deutlich niedriger. Darüber hinaus lagen nicht nur die Mittelwerte, sondern 95% der Werte für die KZV240 unter dem vorhandenen cut-off-Wert für die KZV16.

Die KZV240 hat eine relativ starke, statistisch signifikante Korrelation mit der KZV16 (r = 0,646, p <0,001). Eine mittlere, obwohl statistisch signifikante Korrelation (r = 0,373, p <0,001) zwischen Schwangerschaftswoche (SSW) und KZV240 wurde dokumentiert, während die Korrelation zwischen KZV16 und SSW vernachlässig war.

In den ersten 24h nach der ersten intramuskulären Kortikosteroidgabe wurde eine vorübergehende Zunahme sowohl der KZV240 als auch der KZV16 dokumentiert, im Vergleich zu den KZV240 und KZV16 ohne RDS-Prophylaxe oder mindestens 72h danach. Darauf folgte eine vorübergehende Abnahme sowohl der

KZV240 als auch der KZV16 zwischen 24h und 72h nach der ersten intramuskulären Kortikosteroidgabe.

Unsere Ergebnisse bestätigten unsere Hypothese und erlaubten uns, die Referenzwerte für die KZV240 zu berechnen. Es ist extrem wichtig für jeden Arzt, der den neuen Algorithmus in seiner alltäglichen Praxis verwendet, zu wissen, dass die Normalwerte für die KZV240 (nicht nur der Mittelwert, sondern auch die 95. Perzentile) unterhalb der bislang etablierten cut-off-Werte für die KZV16 liegen. Dies unterstreicht die Tatsache, dass bei der Interpretation der KZV des cCTGs der verwendete Algorithmus berücksichtigt werden sollte. Ansonsten besteht die Gefahr von unnötigen, iatrogenen, vorzeitigen Entbindungen mit allen damit verbundenen Risiken.

INTRODUCTION

Intrauterine Growth Restriction

Timely recognition and appropriate management of high risk pregnancies are of paramount importance for every obstetrician. Small for gestational age (SGA) fetuses constitute a major part of pregnancies at increased risk for poor perinatal outcome. However, from the pool of the SGA fetuses, the ones with normal placental function are not at risk for adverse perinatal events [Soothill et al, 1999]. These constitutionally small fetuses must be differentiated from the ones with Intrauterine Growth Restriction (IUGR).

IUGR is characterised by placental dysfunction and carries an increased risk of perinatal mortality and morbidity [Illanes and Soothill, 2004]. IUGR is shown to be associated with stillbirth [Cnattingius et al, 1998], birth hypoxia [McIntire, 1999], increased prevalence of neonatal complications [Bernstein et al, 2000], impaired neurodevelopment [Kok et al 1998; Roth et al, 1999], adult hypertension [Lackland, 2003] and type II diabetes mellitus [Hales and Ozanne, 2003].

The initial screening method for the early recognition of IUGR fetuses is based on a combination of biometric parameters with fetal Doppler values. Sonographic fetometry is used to identify SGA fetuses and fetal Doppler flow velocimetry is in turn used as a direct indicator of placental dysfunction, in order to recognise the IUGR fetuses [Baschat et al, 2001]. Progressively abnormal pulsatile index in the umbilical and / or middle cerebral artery is a sign of placental insufficiency with increasing hypoxemia and/or hypoxia, whereas an abnormal Ductus venosus waveform usually correlates with acute changes present in advanced stages of fetal compromise [Figueras and Gardosi, 2011].

Once the diagnosis of IUGR has been made, the focus is shifted to the appropriate monitoring and accordingly timing of delivery. In cases of late IUGR, where the risk of prolongation of pregnancy overcomes the benefits, timing of delivery is a relatively simple decision. However, in cases of early IUGR, this decision can become a very difficult task, in trying to balance the risk between

potential iatrogenic prematurity and prolongation of the exposure to an adverse intrauterine milieu.

At this point, cardiotocography (CTG) has been employed as a pivotal tool in the day-to-day monitoring of the antenatal well-being of the IUGR fetus [Visser and Huisjes, 1977]. Since the first introduction of CTG in the antenatal surveillance of high risk pregnancies, there has been great progress in the recording of the fetal heart rate (FHR) as well as its interpretation. The advances in the area of Information & Communication Technology has allowed for the evolution of the traditional CTG to the nowadays widely spreading implementation of computerised CTG (cCTG) in the clinical practice.

Cardiotocography

Cardiotocography is the continuous and simultaneous recording of the fetal heart rate (FHR) and the maternal contractions (Figure 1). CTG is a method widely used for the assessment of fetal well-being, predominantly in pregnancies with increased risk of complications, such as IUGR [Grivell et al, 2015].

Since 1766, when the auscultation of the FHR was reported for the first time by Wrisberg [Roederer, 1766], various technological advancements have allowed for the monitoring of the fetal heart rate and of the uterine contractions to become what is nowadays widely known and used as CTG.

The development of CTG is attributed mainly to three researchers: Caldeyro-Barcia, Hon and Hammacher.

Caldeyro-Barcia studied in the early 50s' the physiology of the uterine contractions, through the insertion of a catheter in the amniotic cavity [Caldeyro-Barcia et al, 1959; Alvarez and Caldeyro-Barcia, 1954]. At about the same time, Hon introduced the monitoring of the fetal heart rate using an electrode inserted through the vagina and attached to the fetal scalp [Hon, 1958; Hon, 1966].

The great breakthrough occurred in the mid-60s', when Hammacher, in cooperation with Hewlett-Packard, achieved to document the fetal heart rate via external phonocardiotocography. Calculation of the fetal heart rate was made

possible through measurement of the fetal pulse interval [Hammacher, 1962; Hammacher 1967; Hammacher, 1969].
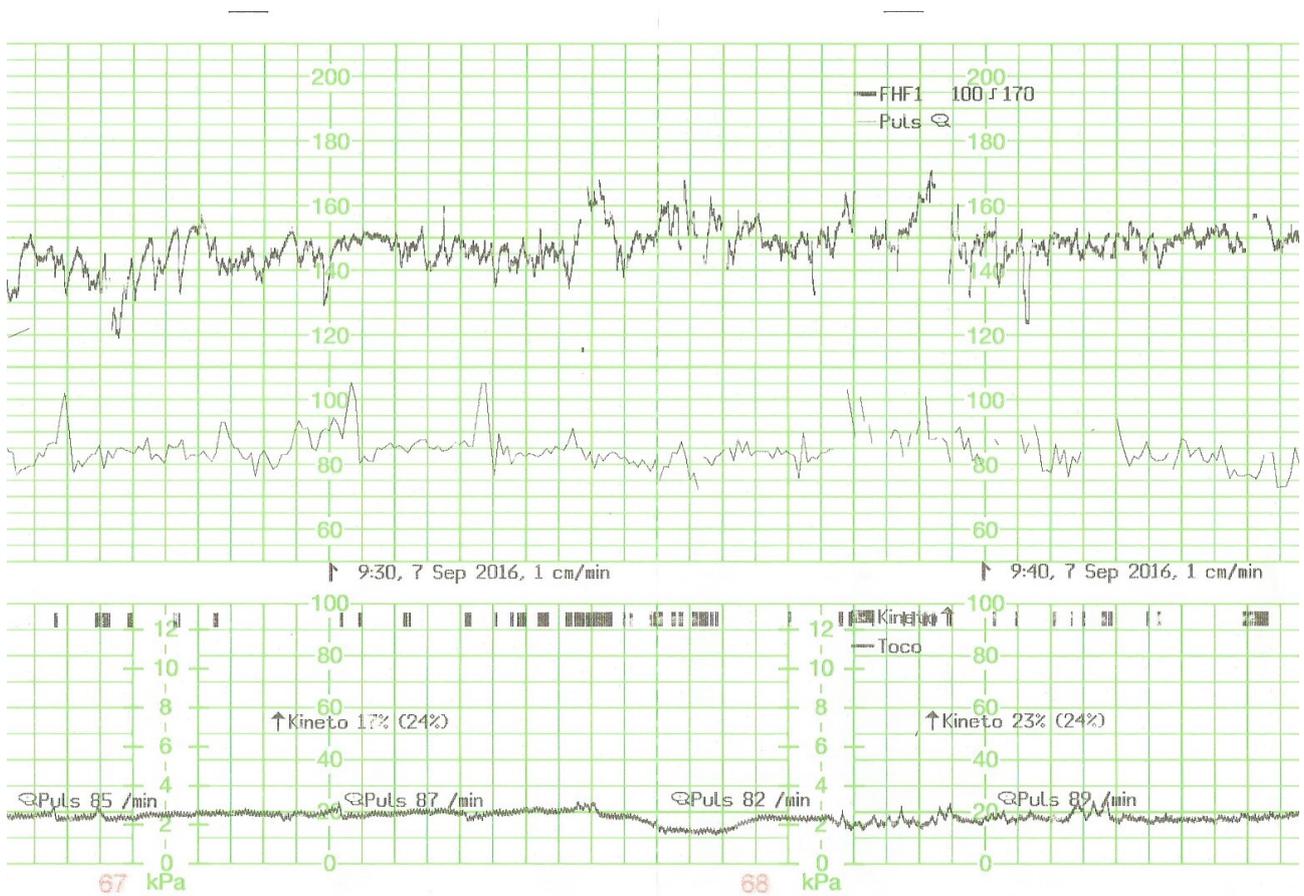
Figure 1: example of a normal CTG trace

The evolution of the Doppler technology enabled great progress in the monitoring of the fetal heart rate. In the 70s', the use of a wide-angled ultrasound transducer on the abdominal wall of the mother for the monitoring of the FHR found widespread use [Hop and Heinrich, 1979].

Those developments led to what is nowadays known as CTG, the continuous recording of the FHR and of the uterine activity. The fetal heart rate is obtained via an ultrasound transducer placed on the mother's abdomen and the uterine activity is registered via a second transducer placed also on the mother's abdomen, over the uterine fundus (Figure 2). Both traces are documented simultaneously onto a paper strip [Alfirevic et al, 2013].

Figure 2: Ultrasound transducer for the FHR and tocometer

The components of the fetal heart rate that are routinely assessed are baseline rate, baseline variability, accelerations and decelerations. There are various criteria for the interpretation of the CTG. Widely used among those are the Fischer-Score (Table 1) [Fischer et al, 1976] and the FIGO-Score (Table 2) [Ayres-de-Campos et al, 2015]. All these score-systems use the optical, subjective evaluation of the above mentioned components of the fetal heart rate as an indicator of fetal well-being.

The established normal values for the above named parameters are [RCOG, 2001]:

- oscillation amplitude of the FHR more than 5 bpm

- baseline of the FHR between 110 and 160 bpm (beats per minute)

- presence of at least two accelerations of the FHR in 20 minutes

- absence of decelerations.

The use of the above parameters derives from the physiology of the fetal cardiac function and the regulation of the FHR from the fetal autonomous nervous system [Kamath and Fallen, 1993]. As the physiological mechanisms that regulate the FHR depend on an intact central nervous system, the failure of the fetus to demonstrate

a normal pattern of FHR may be the result of grave hypoxic brain damage [ACOG, 2000].

	0 points	1 point	2 points
Baseline	<100 or >180 bpm	100-110 or 160-180 bpm	110-160 bpm
Bandwidth	<5	5-10 or >30	10-30
Zero-crossings	<2	2-6	>6
Accelerations	none	periodic	sporadic
Decelerations	late	early	none, variable
8-10 points	physiologic fetal condition		
5-7 points	questionable fetal condition		
0-4 points	critical fetal condition		

Table 1: Fischer-Score for the antepartum visual interpretation of the CTG

	Normal	Suspicious	Pathological
Baseline	110-160 bpm		<100 bpm
Variability	5-25 bpm	Lacking at least one characteristic of normality, but with no pathological features	Reduced variability for > 50 min, increased variability for >30 min, sinusoidal pattern for > 30 min
Decelerations	No repetitive decelerations		Repetitive late or prolonged decelerations during > 30 min or 20 min if reduced variability or one prolonged deceleration > 5 min
	no fetal hypoxia/ acidosis	**low probability of fetal hypoxia/acidosis**	**high probability of fetal hypoxia/acidosis**

Table 2: FIGO-Score for the intrapartum visual interpretation of the CTG

CTG is a very sensitive screening test, with a high negative predictive value, lacks however on specificity and positive predictive value. A normal, reactive CTG trace is reassuring, as it reflects a normal, uncompromised fetus. On the other hand, an abnormal CTG trace can reflect a range of fetal conditions, not all of which are necessarily the result of fetal hypoxemia or metabolical acidosis [Spencer, 1993].

A major restriction of CTG is the intra-observer variability of its subjective visual assessment and the lack of reproducibility of its results [Bernardes et al, 1997; Devane and Lalor, 2005]. The interpretation of the CTG is highly dependent on the level of expertise of the clinician and even experts don't always come in agreement when evaluating series of CTGs [Hruban et al, 2015]. And while the level of agreement is high when it comes to normal CTG traces, it drastically drops with suspect or pathological findings, when further intervention is needed [Ayres-de-Campos et al, 1999]. It is furthermore very intriguing, that a physician's interpretation of a CTG-trace and thus hers / his further recommendations vary significantly, depending on hers / his knowledge of fetal outcome [Reif et al, 2016].

Remarkably, despite traditional CTG being routinely used in the antenatal monitoring of high-risk pregnancies, such as pregnancies complicated with IUGR, there isn't enough evidence to support its effectiveness in improving the perinatal outcome [Brown et al, 1982; Kidd et al, 1985; Grivell et al, 2015], although there is a documented association between abnormal CTG traces and poor perinatal outcome [Lumley et al, 1983]. On the other hand, antenatal CTG monitoring has been shown to reduce inpatient management of high-risk pregnancies, when a reassuring trace was obtained [Flynn et al 1982].

In order to overcome these shortcomings of traditional antenatal CTG monitoring, the need for an advanced, electronic and objective assessment of the fetal heart rate has led to the development of cCTG.

Computerised cardiotocography

In an effort to objectify the interpretation and evaluation of CTG, Dawes and Redman introduced in the 1980s the computerised analysis of the CTG [Dawes et al, 1991; Dawes et al, 1991]. They developed a system, also known as Oxford system, which is implemented in the Sonicaid Fetalcare monitor and takes into consideration a number of numerical, computer based, parameters known as Dawes-Redman criteria (Table 3) [Pardey et al 2002]. Those criteria can be broadly summarised as:

- STV of 3ms or greater

- No evidence of a sinusoidal rhythm

- At least one episode of high variation

- No large or repeated decelerations

- Accelerations and / or fetal movements

- No evidence of a baseline misfit

- A normal basal heart rate.

At least one episode of high variation during the recording
STV >3ms (but average LTV of all episodes of high variation >3rd percentile for the gestational age when STV 3-4,5ms)
No evidence of high-frequency sinusoidal rhythm
At least one acceleration or fetal movement rate >20/h and average LTV of all episodes of high variation >10th percentile for the gestational age
At least one fetal movement or three accelerations
No deceleration of >20 lost beats if recording <30min, no more than one deceleration of 21-100 lost beats if recording >30min, no decelerations at all of >100 lost beats
Basal heart rate 116-160 bpm if recording <30min
LTV within 3 SDs of its estimated value or STV>5ms and one episode of high variation with >0,5 fetal movements/min and basal heart rate ≥120 bpm and signal loss <30%
Final epoch of the recording not part of a deceleration if recording <60min or deceleration not >20 lost beats if recording 60min
No suspected artefacts at the end of the recording if recording <60min

Table 3: Oxford system's criteria for normality

If all of the above mentioned criteria are met after the first 10 minutes of the recording, the system will report "Criteria Met" and the monitoring can be stopped, as the trace can be interpreted as reassuring. If after 10 minutes the criteria are not met, then the monitoring should continue and the trace will be reevaluated every 20 minutes and will eventually stop to report "Criteria Met" or go on for 60 minutes if the criteria are not met. If the criteria are never met in the period of 60 minutes, then the monitoring will stop with the report "Criteria Not Met", in which case the trace is non-reassuring and further clinical evaluation and eventually action is

needed [Dawes et al, 1991]. It is of paramount importance to await the full 60 minutes before interpreting a trace as non-reassuring, as a fetal sleep circle can last up to 50 minutes, in which period there is no reactive fetal heart pattern [Dawes et al, 1996]. It has been demonstrated, that many of the above named parameters have a direct, independent correlation to the fetal outcome [Galazios et al, 2010].

The development of cCTG offered many advantages in comparison to traditional CTG. First of all it made possible to eliminate the intra-observer variability and improve the reproducibility of the results, as the interpretation of the CTG trace is performed by a computer program [Chen et al, 2014]. Another important advancement was the reducing of the recording time. As mentioned above, a CTG trace can often be evaluated as reassuring in only 10 minutes, whereas a traditional CTG needs to be at least 20 to 30 minutes long in order to be evaluable. Last but not least, the cCTG technology allowed for the determination of FHR parameters such as long- and short-term variation (LTV and STV) that cannot otherwise be assessed visually [Dawes et al, 1991].

The effectiveness of cCTG in comparison to traditional CTG has been mainly studied in high risk pregnancies, such as pregnancies complicated by IUGR, hypertension, preeclampsia, diabetes, etc. There are two major studies, which evaluated the effects of cCTG in comparison to traditional CTG in terms of perinatal outcome, caesarean section rates, number of diagnostic interventions and time spent in antenatal monitoring [Bracero et al, 1999; Steyn and Odenaal, 1997]. Both studies showed an improvement of perinatal outcome, although the caesarean section rates did not differ between the two groups. Furthermore, a reduction in the number of diagnostic interventions as well as time spent in antenatal monitoring was confirmed in the group of cCTG.

All of the above advantages of cCTG have led to its more and more widespread implementation in the clinical praxis. However, there is still a long way to go, before cCTG replaces traditional CTG as part of the routine antenatal monitoring in every clinic and every hospital. For the time being, cCTG is mainly implemented in major perinatal centres and university hospitals, which manage a large number of high

risk pregnancies, as part of the routine antenatal monitoring of these high risk cases.

Short term variation of the fetal heart rate

One of the parameters of the Dawes-Redman criteria is the Short Term Variation (STV) of the FHR. STV is one of the most significant parameters, especially in the antenatal monitoring of IUGR fetuses [Snijders et al, 1992].

STV is a measure of the micro fluctuations of the FHR. In the Dawes-Redman system, STV is calculated by dividing each minute into 16 segments, each one being 3,75 seconds long and including 7-10 fetal heartbeats, or 6-9 pulse intervals. The average pulse interval in each section is calculated and the STV derives from the difference of the average pulse intervals between two sections. For that reason the STV is calculated in milliseconds (ms) [Sonicaid Fetalcare Clinical Application Guide]. This calculated STV does not however equal the beat-to-beat variation of the FHR, which cannot be measured with external Doppler ultrasound technology.

The STV is independent from the baseline of the FHR. Two major factors that can influence the STV are the sleep circle of the fetus and the administration of corticosteroids to induce lung maturation.

It is normal for a fetus to have a long quiet period as in deep sleep, where the FHR is relatively flat with low STV. As such normal episodes of deep sleep can last up to 40 or 50 minutes, it is important to wait for at least 60 minutes before a trace with a low STV is characterised as abnormal [Dawes et al, 1996].

Furthermore, the administration of corticosteroids in the context of respiratory distress syndrome (RDS) prophylaxis in cases of threatened premature delivery, has a similar impact on the STV, as it can lead to transiently reduced STV. For that reason it is important to disregard the possible STV alterations that occur during the first 3 days after the administration of the RDS prophylaxis [Rotmensch et al, 2005].

It has already been shown, early on that in cases of non-reactive fetal trace (without episodes of high variation) low STV is strongly linked to developing metabolic acidaemia and impending intrauterine death [Street et al, 1991]. A low

STV is usually seen in chronically stressed IUGR fetuses. A series of important studies has demonstrated, that, when monitoring fetuses with preterm IUGR, STV changes can and should play an important role on the timing of delivery.

The first major study on the role of STV in the monitoring of IUGR fetuses was conducted by Street et al in 1991, as until that time the role of LTV was more prominently studied. This study group was able to demonstrate, that the STV has a positive correlation to the LTV, although STV can better recognise metabolic acidemia, by STV values under 3 ms. Furthermore, all terminal cases can be identified, when the STV drops under 2,5 ms [Street et al, 1991].

The study group of Dawes et al followed one year later to demonstrate, that by STV values under 2,6 ms, 35% of all monitored fetuses will have a metabolic academia on point of birth, or will even have suffered intrauterine demise [Dawes et al, 1992].

Guzman et al confirmed in 1996, that low STV in IUGR fetuses has a significant correlation to umbilical artery pH after birth and could consistently predict academia at birth. This study group set however the cut-off value of the STV higher, at 3,5 ms [Guzman et al, 1996].

In 2001 Hecher et al demonstrated that the STV together with the pulsatility index of the ductus venosus (DVPI) are the most important markers of impending fetal acidosis and should play a paramount role on the timing of the delivery of IUGR fetuses. They used in their study a cut-off value of 3 ms [Hecher et al, 2001].

In 2004 Anceschi et al set an even higher cut-off for the STV by 4,5 ms. They suggested that STV values under this cut-off can predict a developing metabolic acidaemia with 100% sensitivity and 70% specificity [Anceschi et al, 2004].

Serra et al in 2008 confirmed for one more time the pivotal role of the STV as an important predictor of the perinatal outcome of IUGR fetuses. The cut-off value was set again by 3 ms [Serra et al, 2008].

The latest development in the role of STV in the monitoring of IUGR fetuses took place in 2015, with the final disclosure of the results of the TRUFFLE study. According to the results of this study, even when the primary monitoring of IUGR

fetuses and decision making regarding the timing of delivery is based on other parameters, such as fetal Doppler values, the STV should always be taken into consideration and even be used as a safety net. Delivery shouldn't be delayed after the STV has reached a critical low (2,6 ms for 26.0 to 28.9 weeks of gestation and 3 ms for 29.0 to 32.0 weeks of gestation), even when the other monitored parameters are still normal [Lees et al, 2015].

To add to the TRUFFLE-Study, a secondary analysis of its results by Wolf et al. in 2016, demonstrated that it is essential to monitor the STV of IUGR fetuses even more than once daily. Furthermore, they confirmed that it is safe to wait for a low STV, as long as the DVPI remains normal [Wolf et al, 2016].

Challenges in the interpretation of computerised CTG

Since Cardiotocography was first developed and used in clinical practice until the present day, many and major advancements took place that helped evolve CTG into the indispensable diagnostic and monitoring tool that it constitutes nowadays.

A pivotal step in this way was the introduction of cCTG in the 1980s, which opened new horizons to the objective and reproducible monitoring, especially of high risk pregnancies, such as pregnancies complicated with IUGR.

After the TRUFFLE-Study, the pivotal role of cCTG, and especially of the STV, has been brought in the spotlight in the management of IUGR.

Every physician is put before an extremely difficult and at the same time of paramount importance decision, when it comes to the timing of the delivery of a premature fetus with IUGR. In this direction, every tool that can aid with this decision in an objective and reproducible manner is invaluable.

It appears that the STV of the FHR can play, at least part of, this role. The available studies up until now support this fact. However, most of the later, including the multicenter TRUFFLE-Study, limit their results between the 26th and 32nd week of gestation. Thus, it is crucial that research in this field does not cease, that the studied spectrum becomes wider and that further emerging technological developments be constantly implemented into the existing methods.

Potential restrictions of the currently available methods for the antepartum monitoring of IUGR, and especially early-IUGR, fetuses should be recognised. For instance, all of the above mentioned studies draw their results based on the Dawes-Redman algorithm, which is however only implemented in the Sonicaid Fetalcare monitor. It remains unclear, if the same rules and normal values apply to parameters such as the STV, calculated using other commercially available monitoring systems. Until this grey zone is clarified through more studies, it is important for every physician to know, that only parameters that are calculated with the Dawes-Redman system can be compared to the ones described in the current literature [Kouskouti et al, 2017].

It is therefore essential, that effort should be put in the evolution of the already existing methods or even the development of new, more refined ones.

RESEARCH QUESTION

Cardiotocography (CTG) constitutes a pivotal element in the monitoring of the antenatal wellbeing of the fetus [Grivell et al, 2015]. Traditionally, visual analysis and subjective interpretation of the CTG-tracings have been used to guide clinical decisions, such as time point and mode of delivery. Visual analysis based on relevant score systems (e.g. FIGO, FISHER) is very effective in detecting a "terminal trace" when the fetal heart rate (FHR) is flat with repetitive shallow decelerations [Visser and Huisjes, 1977]. However, this is a rare and extreme situation and the fetuses that manifest this kind of trace are already severely affected. More commonly the trace abnormalities are subtle, which makes the visual interpretation difficult and often inaccurate [Bernardes et al, 1997].

Computerised analysis of the fetal heart rate (FHR), introduced more than two decades ago, has conferred important advantages in the evaluation of the fetal status antenatally [Dawes et al, 1991]. The numerical measures of the FHR pattern derived from the computerised analysis have been shown to correlate with other

objective parameters of fetal health. Quantitative results, presented in a consistent manner, allow for improved accuracy and more efficient process of information and, therefore, shorter recording time [Dawes et al, 1991].

Currently, one of the most widespread systems for cCTG analysis is the Dawes-Redman system (Sonicaid Fetalcare by Huntleigh Healthcare). This system takes into consideration a number of numerical, computer based, parameters known as Dawes-Redman criteria [Pardey et al, 2002], with Short Term Variation (STV) of the FHR being one of the most significant, especially in the antenatal monitoring of fetuses with intrauterine growth restriction (IUGR) [Dawes et al, 1990; Snijders et al, 1992].

IUGR is one of the most significant diagnosis that an obstetrician needs to be able to make and consequently monitor throughout a pregnancy. From the major pool of small for gestational age (SGA) fetuses, the ones with IUGR are characterised by placental dysfunction and carry an increased risk of perinatal mortality and morbidity. IUGR has been associated with stillbirth, birth hypoxia, increased prevalence of neonatal complications, impaired neurodevelopment, adult hypertension and type II diabetes mellitus [Illanes and Soothill, 2004].

The diagnosis of IUGR is based on a combination of abnormal biometric parameters with abnormal fetal Doppler values. A direct indicator of placental dysfunction, which serves for the initial diagnosis and the subsequent monitoring in cases of IUGR, is the fetal Doppler flow velocimetry in certain vessels, according to fetal state, which measures the regional blood flow changes that occur in case of fetal hypoxemia [Baschat et al, 2001]. Once the diagnosis of IUGR has been established, CTG, and especially the STV of the FHR as part of the cCTG, plays, along with Doppler sonography, a major role in the subsequent monitoring and timing of delivery of IUGR fetuses [Snijders et al, 1992].

STV is a measure of the microfluctuations of the FHR. It is independent of the fetal baseline and, in cases of non-reactive fetal trace (without episodes of high variation), low STV is strongly linked to developing metabolic acidemia and impending intrauterine death [Street et al, 1991]. A low STV is usually seen in

chronically stressed IUGR fetuses [Dawes et al, 1992; Guzman et al, 1996]. However, a trace with low STV may also correspond to a fetus having a long quiet period, as in deep sleep, where the FHR is relatively flat with low STV. As such episodes of deep sleep can last up to 40 or 50 minutes, it is important to wait for at least 1 hour before such a trace with a low STV is characterised as abnormal [Dawes et al, 1996]. Furthermore, the administration of corticosteroids in cases of respiratory distress syndrome (RDS) prophylaxis has a similar impact on the STV, as it leads to transiently increased STV within the first 24h followed by transiently reduced STV until the first 72h. For that reason, the STV alterations registered during the time of RDS prophylaxis should not be taken into consideration for the clinical decision making [Mulder et al, 1994; Rotmensch et al, 2005].

It has been shown that STV changes can and should play an important role in the timing of delivery of fetuses with preterm IUGR, even when the primary monitoring and decision making is based on other parameters, such as fetal Doppler values [Hecher et al, 2001]. In cases of IUGR fetuses, delivery shouldn't be delayed after the STV has reached a critically low value, even when the other monitored parameters are still normal [Anceschi et al, 2004; Serraet al, 2008; Lees et al, 2015].

In the Dawes-Redman system, the STV is measured by dividing each minute into 16 segments, each one being 3,75 seconds long and including 7-10 fetal heartbeats or 6-9 pulse intervals (STV16). The average pulse interval in each segment is calculated and the difference of those pulse intervals between two segments determines the STV [Sonicaid Fetalcare Clinical Application Guide]. From the above, it is clear that the STV16 does not equal the beat-to-beat variation of the FHR.

Theoretically, measurement of the pulse interval in much smaller time fractions, so that every heartbeat would be taken into consideration (instead of one every 7-10 heartbeats), would lead to a more accurate approximation of the beat to beat variation with significant advantages for the antenatal monitoring of the fetus.

New developments in Information and Communication Technology (ICT) have led to the development of new algorithms, which take into consideration every single heartbeat for the calculation of the STV [Amorim-Costa et al, 2016]. One of them is the IntelliSpace Perinatal by Philips Medical, which measures the STV by dividing each minute into 240 segments (STV240), thus attempting to better approximate the beat-to-beat variation of the FHR. The pulse interval in each section is then calculated (with redundant values coming from the same pulse being automatically disregarded) and the difference of those pulse intervals determines the STV240.

One of the problems that arise after the development of a new computing algorithm for the calculation of any clinical parameter is the lack of reference values, based on a clinical database. Without reference values for the specific algorithm, no clinical consequences can be drawn [Siest et al, 2013]. It has already been shown, that, when calculated with the use of different algorithms, the normal values for the STV differ to the ones known for the Dawes-Redman system [Amorim-Costa et al, 2016].

An effort in our department to implement the existing cut-off values of the STV16 as reference values for the new STV240 algorithm has resulted in highly abnormal findings, with STV240-values significantly below the cut-off values of the STV16 [Serra et al, 2009]. This event was not only noted in IUGR cases, but also in healthy, appropriate for gestational age (AGA) fetuses. Therefore, despite their accuracy, the values derived from the new algorithm cannot contribute to the decision making process, as they cannot be readily categorised as normal or abnormal.

This observation led to the formation of the hypothesis, that the reference values for the STV240 should be different, and, more precisely, lower in comparison to the existing reference values for the STV16. This hypothesis is not only based on clinical observation. The discrepancy noted between the two different algorithms is also logically sound, as it is to be expected that the variation between two subsequent beats will be notably lower as the variation between 7-10 subsequent heartbeats.

As the new algorithm is being implemented in the clinical practice it is important to have reference values. Therefore, we conducted an observational, prospective clinical study in order to develop clinically relevant reference values for the STV240 and compare the reference values for the STV240 to the ones for the STV16.

At the same time, we studied the effects of RDS prophylaxis on STV240 and STV16 in order to verify if the known transient effects of corticosteroids on the STV could also be detected with the new algorithm for the STV240.

Our results will hopefully allow for more accurate interpretation of the computerised CTG findings and better clinical monitoring of IUGR fetuses.

METHODS

Study design

This was a single-center, non-interventional study. The acquisition of the data followed in a prospective manner. The CTG traces that were acquired as part of the routine antenatal monitoring of our pregnant patients, were gathered and subsequently analysed with both algorithms (STV240 and STV16).

Study population

The CTG traces were collected from September 2015 until October 2016 in the antenatal department of the Klinik Hallerwiese, Nuremberg, Germany. The study included CTG traces starting from 24.0 until 33.6 weeks of gestation.

Only CTG traces of appropriate for gestational age (AGA) fetuses with normal fetal and maternal Doppler parameters (umbilical artery (UA), middle cerebral artery (MCA), uterine artery (UtA)) were included in our study. In order to assure the fulfilment of this prerequisite, every patient was subjected to a thorough ultrasound examination with admission to the study. This included: fetal biometry (measurement of the head circumference, abdomen circumference, femur length) and Doppler flow velocimetry of the UA, MCA and UtA (Figure 3).
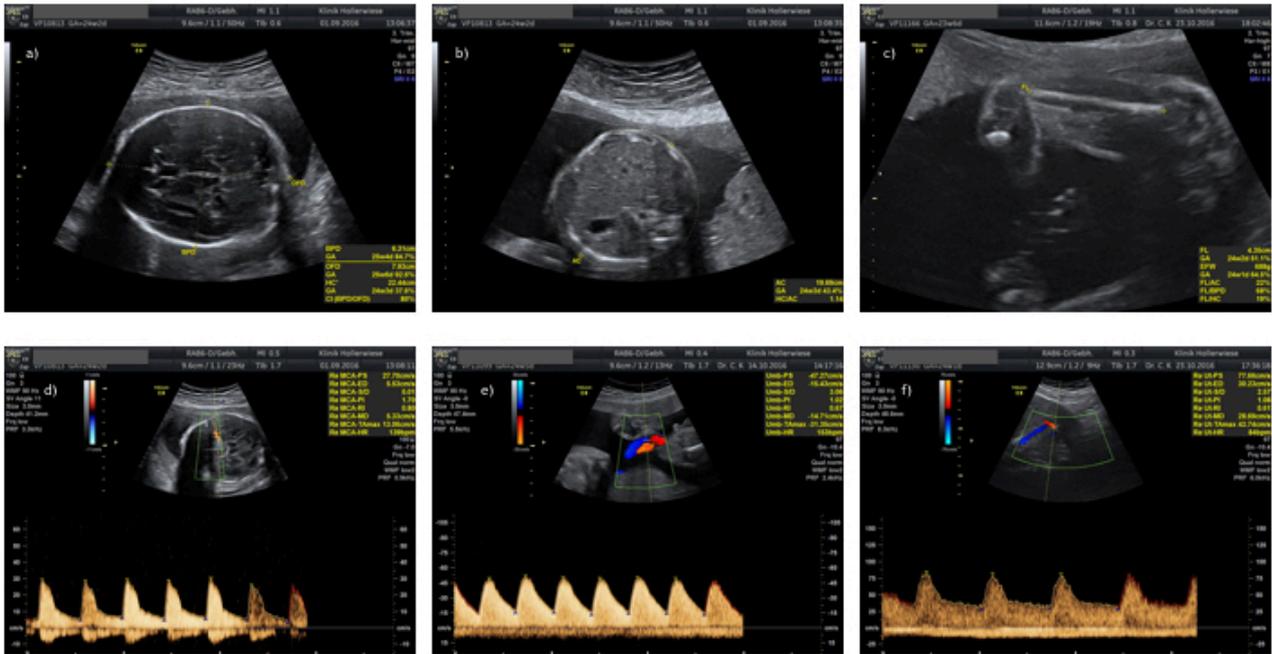
Figure 3: Ultrasound pictures of fetal biometry: a) head circumference, b) abdomen circumference, c) femur length and Doppler flow velocimetry: c) umbilical artery, d) middle cerebral artery e) uterine artery of Patients enrolled in the study

Pregnancies complicated with Diabetes mellitus, hypertensive disease of pregnancy or IUGR were excluded from our normal collective.

In cases where RDS prophylaxis was required, the CTG traces were gathered at a) 0-24h, b) 25-72h and c) at least 72h after the first intramuscular corticosteroid administration. As it is well-known and documented that corticosteroid administration leads to transiently altered STV (Rotmensch, 2005), only the CTG traces gathered at least 72h after the first intramuscular corticosteroid administration were used for the development of the normal ranges. The rest was used for the comparison of the STV under and without the influence of RDS prophylaxis.

Data gathering and FHR analysis

All antenatal patients who receive inpatient care at our department are routinely subjected to at least 2 CTGs per day. From every patient included in the study were recorded: 1. one CTG daily for the first 72h (0-24h, 25-48h and 49-72h) after the first intramuscular corticosteroid administration (in cases where RDS prophylaxis

24

was indicated) and 2. from that point on, or from the beginning in cases where no RDS prophylaxis was administered, one CTG trace per week of gestation, for as long as they were monitored in our antenatal department.

In order to be able to calculate a satisfactory 95% confidence interval for the development of the normal ranges, a minimum of 20 CTG traces without the influence of RDS per week of pregnancy were required.

Figure 4: Avalon Fetal Monitor

All CTG traces were analysed with both the STV240 and the STV16 algorithm in order to acquire comparative data. Data gathering took place at the bedside as part of the standard antenatal CTG recording which is indicated for all pregnant patients who present at our clinic. The CTG devices used for the acquisition of the traces are the Avalon Fetal Monitors of Philips (Figure 4). These are the devices which are used in our everyday clinical practice for the antenatal CTG-monitoring. The Avalon Fetal Monitors are CE marked (Appendix A). The CTG traces were subsequently anonymised and submitted for analysis with both the STV240 algorithm and the STV16 algorithm. In this secondhand, off-line analysis, we received support from Philips Medizin Systeme Böblingen: the anonymised data were submitted to the R&D Department of Philips, which subsequently analysed these traces with both

algorithms and provided us with the resulting STV values. Although the Avalon Fetal Monitors used in our antenatal department can calculate the STV240 in real time at the bedside (Figure 5), we opted for the retrospective analysis, in order to make sure that the STV16 and STV240 resulted from the exact same part of every CTG trace. Each CTG trace was recorded over 60 min, as this is the necessary time in order to assess fetal well-being [14].
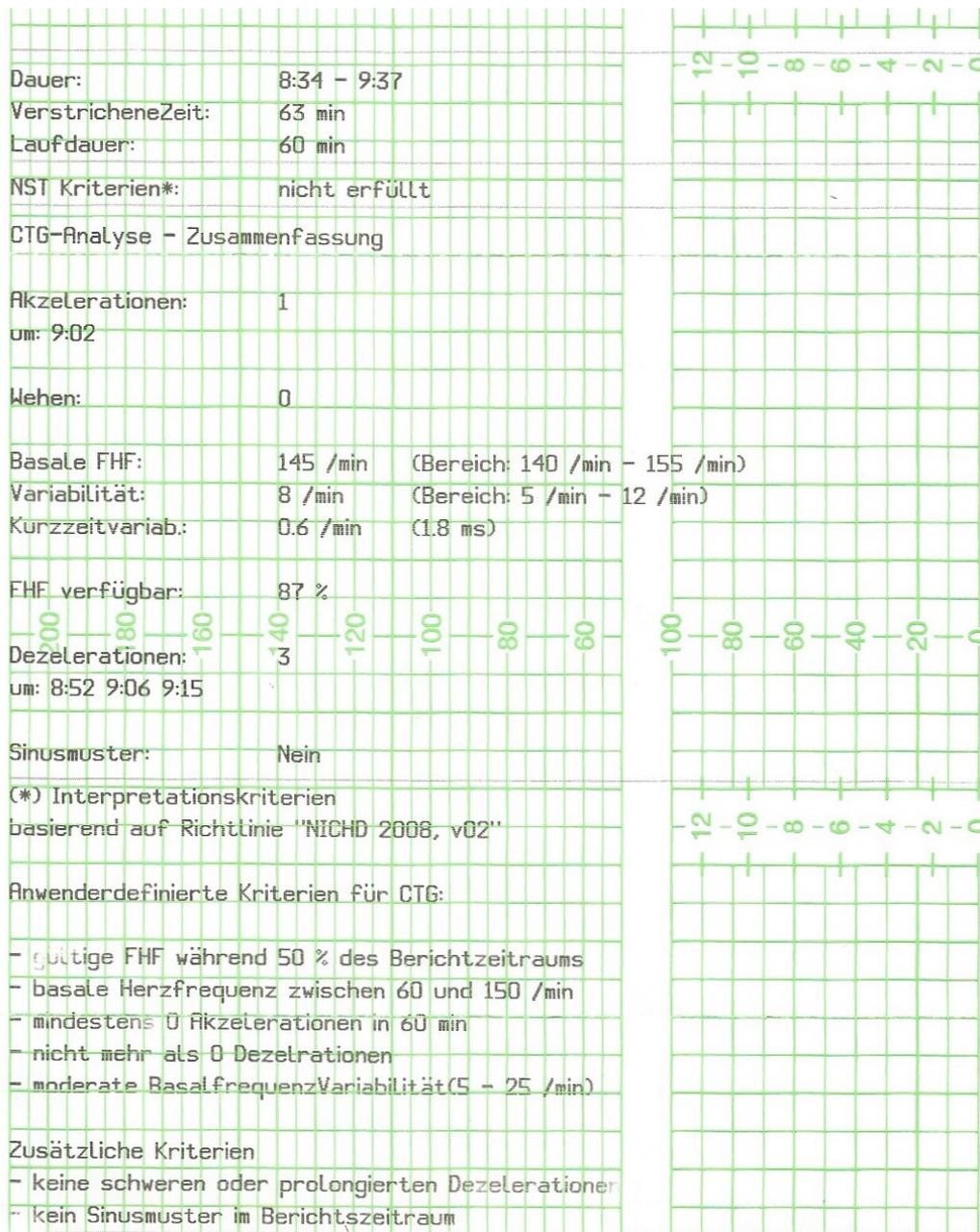

Figure 5: example of a computerised CTG report (non-stress test)

Data processing

The Philips Avalon Fetal Monitors EM20/30 and FM40/50 utilise a proprietary digital communication protocol. The Protocol is used for communication of the monitor base unit with the connected transducers. This closed bus-based communication system supports up to four transducers with real-time data transmission. Each transducer individually performs the signal processing and calculation of one or more parameter values related to the functionality of transducer. The ultrasound Doppler transducer, for instance, calculates the FHR and the fetal movement (FM) based on the received Doppler shifted signal. The update of the FHR values is done in fixed cycles every 16ms, independently of the availability of a new value. This means that a connected transducer is prompted every 16ms to place a data package on the bus. All data packages traveling on the bus are visible and accessible on the bus connectors either for other transducers or for a recording device. The recording device is so to say a special transducer listening to the messages of the other connected transducers. The messages passing between the transducers and the base unit are recorded in a storage device, together with an automatically added date and time annotation. The storage device basically is an exchangeable microSD card with a capacity of up to 2GB. In order to avoid accidental data loss, the data size of the record files is limited in size adjustable portions. Typically a file with the size of 5MB is able to store recordings of 5 minutes. With this file size setting, a session of 60 minutes creates approximately 12 Files. For later session recovery, the file names are automatically controlled depending on a power cycle of the monitor. All files in a directory having an identical pre-fix are considered to be a segment of a session. The SD card has to be replaced by an empty one on a regular basis. Typically the card can hold 1.5 days of continuous recordings. During normal operation of use, this translates to a weekly exchange frequency. After downloading the SD card contents to a PC, further processing can take place. A MatLab program is used to separate all files belonging to a session. The files are subsequently processed to extract raw waves and parameter values. The raw waves are stored in Microsoft wave format and

have no meaning in this context. The parameter values belonging to a session are combined and stored in file format with the extension *.cts. This file format is required by the IntelliSpace Perinatal program for calculation of the STV16 and STV240 values. The *.cts file is ASCII readable and has a structure as shown in Figure 6.

```
#****************************
#CAN Tracefile : 7_00010.can
#FW Revision : A0111
#FW Creation : 090309
#File Size    : 0x2625 * 512
#Volume Name : Nuernb
#Serial Nmbr : DE90300225
#Recording started 10/06/2015 09:40:24
#****************************
FHR1    FHR2    FHR3    TOCO    TocoMP  MHR     FMP     SIG1    SIG2    SIG3    SIGMP   FHR1MODE       FHR2MODE        FHR3MODE        TOCOMODE        MHRMODE WIRELESS
161.25                  19.9    108.95  108.95  0       1                       2       1               9               5               0
161.25                  20.4    109.00  109.00  0       1                       2       1               9               5               0
161.25                  20.8    109.05  109.05  1       1                       2       1               9               5               0
161.25                  20.8    109.10  109.10  0       1                       2       1               9               5               0
161.25                  20.5    109.15  109.15  0       1                       2       1               9               5               0
164.00                  20.4    109.20  109.20  1       1                       2       1               9               5               0
```

Figure 6: example of *.cts file

The file contains 7 parameter columns (FHR1 …. FMP).   If a parameter is available, the related column is filled with values. Exactly 4 values are necessary for every second. The resolution of the heart rate values is ¼ bpm. The columns on the left of the TOCO column have no relevance. A visualisation tool allows the Trace reconstruction with different speed and paper settings for quality check purposes and gap calculation. Figure 7 shows a reconstructed beginning of a session with trace gap calculation (yellowish box on the upper left side).
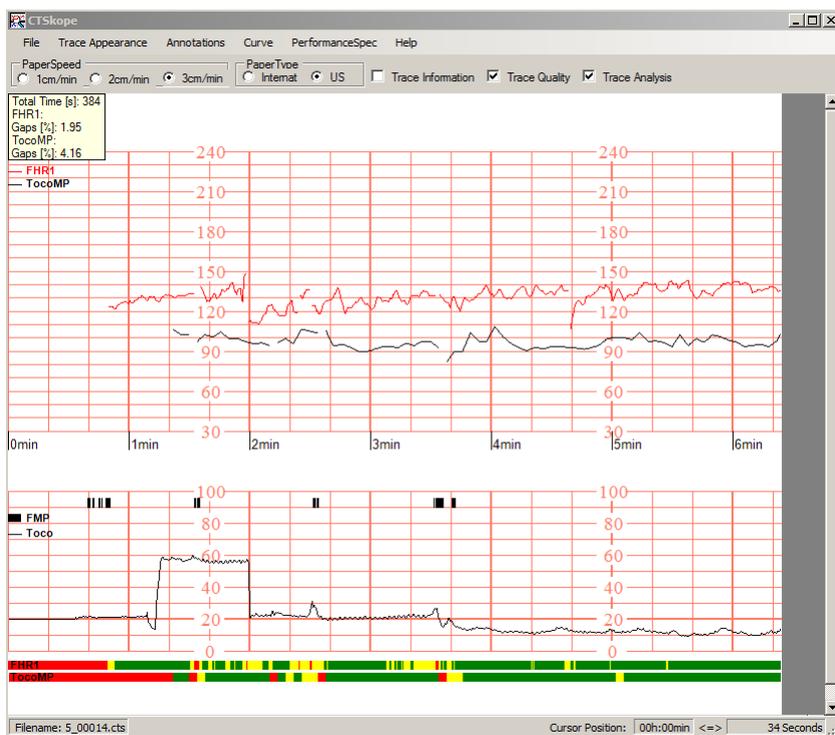

Figure 7: example of a reconstructed trace

As shown in the picture, finding the optimum placement position of an ultrasound transducer is a more or less time-consuming procedure. Heart rate values recorded during this time are either not available or unreliable. The time for finding a stable position can range from a few seconds to a few minutes and can, therefore, influence the values of the gap calculation significantly. The unwanted idle time at the beginning and at the end was manually eliminated by deleting the related rows in the *.cts file. Files with truncated beginning and ending are marked for identification. The *.cts file is the input file for the offline calculation of the STV16 and STV240 values and the gap analysis.

Statistical analysis

The statistical analysis of our data was carried out with "R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2015" (https://www.R-project.org/).

Descriptive statistics (arithmetic means, standard deviation, minimum and maximum, as well as the standard error of the average value) were used to depict the distribution of the STV240 and STV16 pro week of pregnancy. The 95%-confidence interval was calculated from the arithmetic means and the standard error of the average value.

We then performed a Pearson Correlation Coefficient "r" between STV240, STV16 and week of pregnancy.

The correlations between time from RDS prophylaxis and STV240 or STV16 were examined using Kruskal Wallis ANOVA test. All tests with a two-sided p-value <0.05 were considered statistically significant.

Ethical aspects

The study was conducted in compliance with the protocol and the principles of Good Clinical Practice as described in the declaration of Helsinki. The study protocol was submitted to and accepted by the Ethic Committee of the Ludwig-Maximillans-University in Munich (Nr. 391-15).

It was an observational study with neither risks nor benefits for the participants. The examinations required for the study purposes were carried out as part of the routine antenatal monitoring that every pregnant patient receives at our department. All patients participating in the study had to sign an informed consent (Appendix B) form before their data could be used for the purposes of the study.

Data protection was of paramount importance and was respected at the outmost, as all data were anonymised before they left our clinic for further analysis through the ICT department of Philips Medical.

RESULTS

A total of 101 patients between 24.0 and 33.6 week of pregnancy with informed consent were included in the study (93 singleton and 8 twin pregnancies). None of the patients had any of the exclusion criteria (Diabetes mellitus, hypertensive disease of pregnancy or IUGR). All of the fetuses were AGA with normal fetal and maternal Doppler parameters (umbilical artery (UA), middle cerebral artery (MCA), uterine artery (UtA)). This was confirmed by at least one ultrasound examination at admission in the study.

Week of Pregnancy	N (Number of CTG traces included)
25th	21
26th	21
27th	24
28th	30
29th	21
30th	24
31st	22
32nd	20
33rd	24
34th	21
	Total = 228

Table 4: Number of CTG traces included for the development of the normal ranges per week of pregnancy

Reference values

A total of 228 CTG traces from 94 patients (86 singleton and 8 twin pregnancies) were registered and included in the final statistical analysis for the development of the reference values. A minimum of 20 CTG traces were registered per week of pregnancy (Table 4).

The 95% confidence interval was calculated for both the STV240 and the STV16. Table 5 and 6 present in detail the mean values per week of pregnancy for the STV240 and STV16 respectively, as well as the 95% confidence interval for both algorithms.
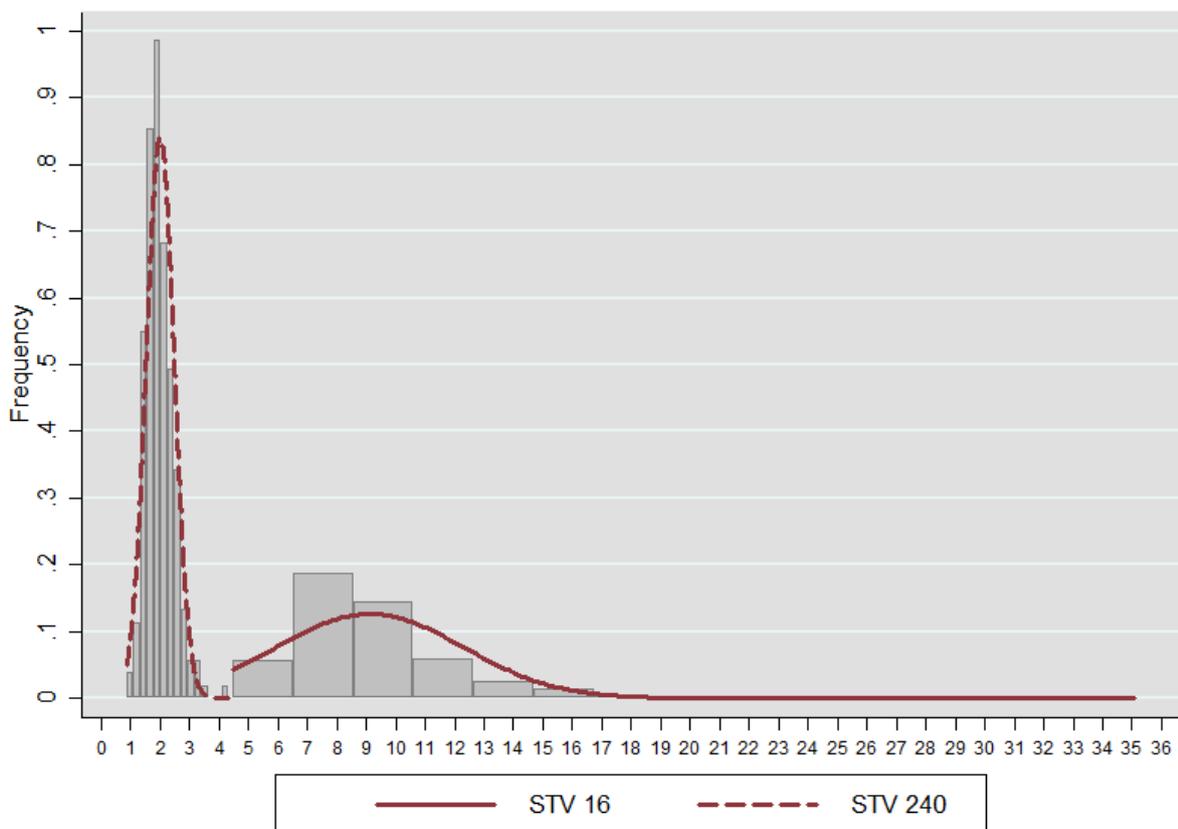

Figure 8: Distribution curves for the STV240 and STV16 in ms irrespective of week of pregnancy

The values of the STV240 were significantly lower in comparison to the ones of the STV16. Moreover, not only the mean values but 95% of the values for the STV240 lay beneath the existent cut-off value for the STV16 (2,6ms for 26.0 to 28.9 weeks of gestation and 3ms for 29.0 to 32.0 weeks of gestation) (Figure 8). Figures 9 and 10 illustrate the normal ranges for the STV240 and STV16 respectively .

31
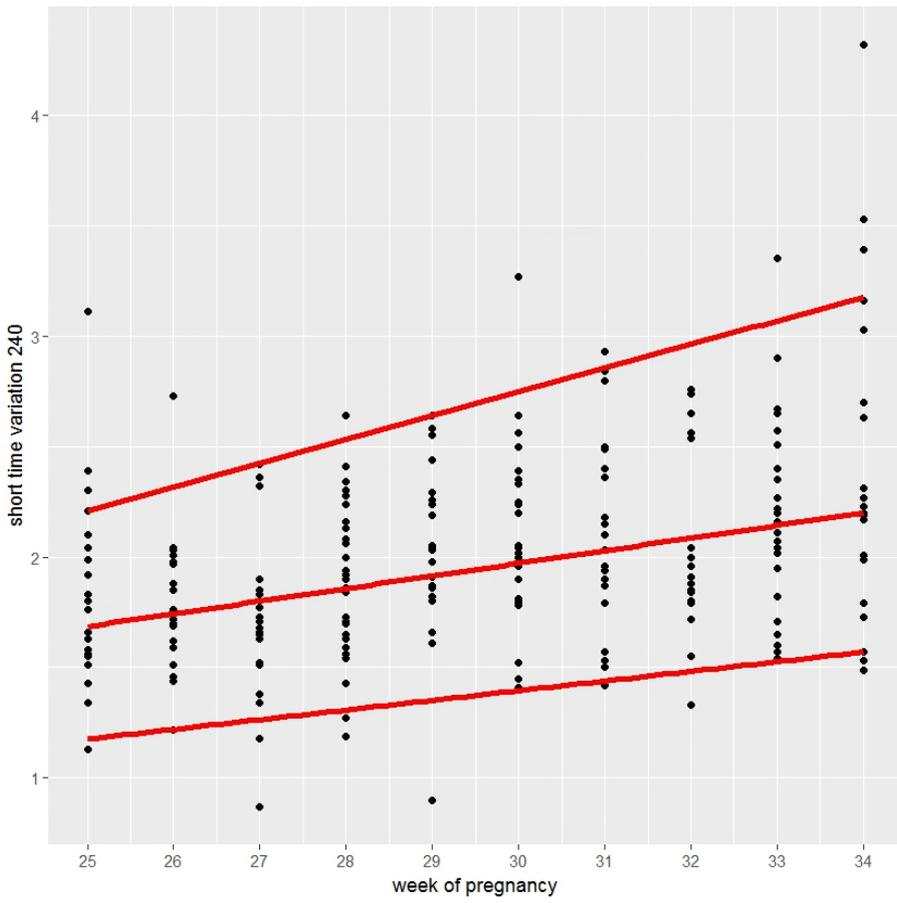
Figure 9: Normal range for STV 240 in ms (5th, 50th, 95th Percentiles)
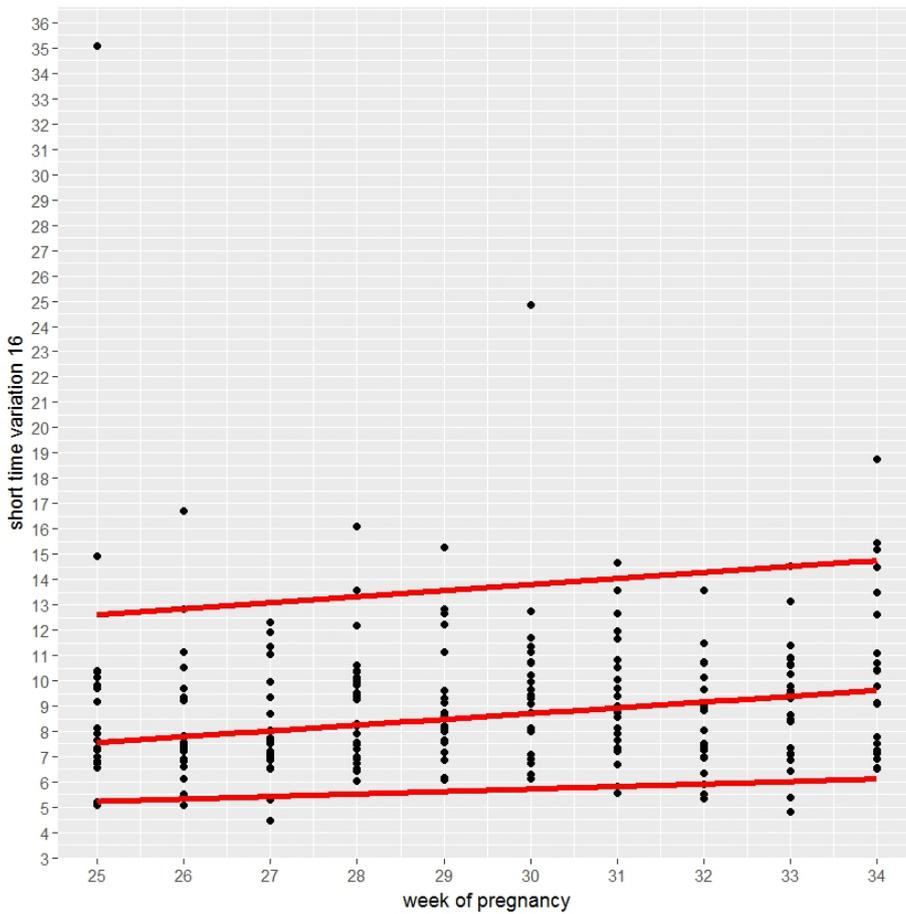
Figure 10: Normal range for STV16 in ms (5th, 50th, 95th Percentiles)

Correlations between STV and week of pregnancy

Table 7 shows the correlations between STV240, STV16 and week of pregnancy. The STV240 has a relative strong, statistically significant correlation with the STV16 (r=0,646, p<0,001). A medium, although statistically significant correlation (r=0,373, p<0,001) between week of pregnancy and STV240 was documented, whereas the correlation between STV16 and week of pregnancy was negligible [Kouskouti et al, 2018].

STV240	relative strong correlation r=0,646, p<0,001	medium correlation r=0,373, p<0,001
	STV16	negligible correlation r=0,088, p=0,09
		Week of Pregnancy

Table 7: Correlations between STV240, STV16 and week of pregnancy

STV under RDS prophylaxis

An additional 57 CTG traces were registered under the influence of RDS prophylaxis and used for the verification of the transient effects of corticosteroids on the STV.

When compared to the STV240 and STV16 without RDS prophylaxis or at least 72h after the first intramuscular corticosteroid administration, a transient increase of both the STV240 and STV16 was documented in the first 24h. This was followed by a transient decrease of both the STV240 and STV16 between 24h and 72h after the first intramuscular corticosteroid injection (Figure 11).

These transient changes of both the STV240 and STV16 over time are statistically significant (p=0,0100 and p=0,0139 respectively, Kruskal-Wallis test) (Table 8).

As illustrated in Figure 11 and Table 8 these changes are more apparent in the case of STV240.
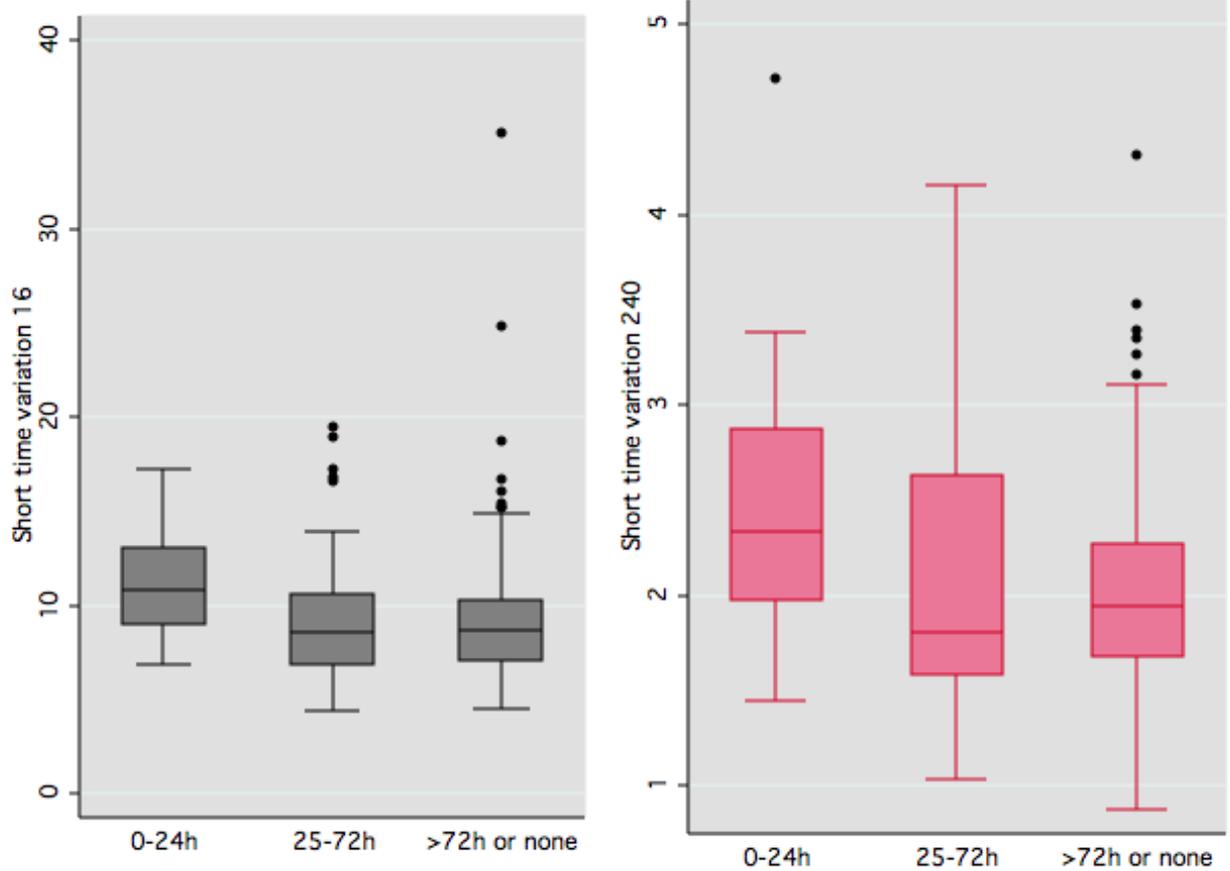
Figure 11: Effect of intramuscular corticosteroid administration in the context of RDS prophylaxis on the STV16 and STV 240 (in ms)

	Mean	Median	Range	SD	p-value (Kruskal-Wallis test)
Short time variation 16					
0-24h	11.076	10.81	6.85-17.25	2.964	0.0139
25-72h	9.533	8.61	4.46-4.46	4.086	
>72h or none	9.112	8.65	5.08-35.09	3.157	
Short time variation 240					
0-24h	2.498	2.34	1.45-4.72	0.764	0.0100
25-72h	2.112	1.81	1.03-4.16	0.782	
>72h or none	2.000	1.94	1.13-4.32	0.474	

Table 8: Correlations between time from RDS prophylaxis and STV240 or STV16

DISCUSSION

The antenatal monitoring of every pregnancy, and especially of high-risk pregnancies, is a very important component of the responsibilities of every obstetrician. Often, especially when complications occur in the early preterm period, this monitoring can become a very challenging task for every clinician faced with the need to decide on the timing of delivery.

IUGR, characterised by placental dysfunction and carrying an increased risk of perinatal mortality and morbidity, is one of the major complications that can occur during a pregnancy. Early IUGR can pose a major monitoring and treating challenge for every obstetrician.

At first, fetuses with IUGR must be singled out from the greater pool of SGA fetuses, on the basis of a combination of biometric parameters with fetal Doppler values. Once the diagnosis of IUGR has been made, the focus shifts to the appropriate monitoring and accordingly timing of delivery. This is where CTG plays its role as a key tool in the day-to-day monitoring of the antenatal well-being of the IUGR fetus.

There are diverse criteria for the interpretation of the CTG, mainly based on the the optical, subjective evaluation of various components of the fetal heart rate as an indicator of fetal well-being. CTG is a very sensitive screening test with a high negative predictive value, has however a high intra-observer variability and lacks on reproducibility of its results.

cCTG was developed more than two decades ago as an advanced, electronic and objective assessment of the fetal heart rate, in order to help overcome these shortcomings of traditional antenatal CTG monitoring. The first cCTG system was introduced in the 1980s by Dawes and Redman and is widely known as the Oxford system. This is implemented in the Sonicaid Fetalcare monitor and takes into consideration a number of numerical, computer based, parameters known as the Dawes-Redman criteria.

One of these criteria is the STV of the FHR. STV, a measure of the micro fluctuations of the FHR, is one of the most significant parameters, especially in the antenatal monitoring of IUGR fetuses. The Dawes-Redman algorithm calculates the STV by dividing each minute into 16 segments, each one being 3,75 seconds long and including 7-10 fetal heartbeats, or 6-9 pulse intervals.

Over the years, a series of important studies has demonstrated that, when monitoring fetuses with preterm IUGR, STV16 values under 3ms correlate positively with the development of metabolic acidemia and should prompt to delivery.

STV16 does not, however, equal the beat-to-beat variation of the FHR. Measurement of the pulse interval in much smaller time fractions, so that every heartbeat would be taken into consideration, would theoretically lead to a more accurate approximation of the beat-to-beat variation, with eventually significant advantages for the fetal antenatal monitoring.

The advancements in the area of ICT have led to the development of new systems for the computerised CTG. One of these is the IntelliSpace Perinatal by Philips Medical. The main innovation that the new system has introduced, is a new algorithm for the calculation of the STV of the FHR. The new algorithm aims to approximate the beat-to-beat variation of the FHR, through measurement of the pulse interval 240 times pro minute (in comparison to 16 times pro minute in the Dawes-Redman algorithm).

The development of a new algorithm for the calculation of any clinical parameter leads to the problem of lacking reference values for the named parameter. An effort in our department to implement the existing cut-off values of the STV16 as reference values for the new STV240 algorithm resulted in highly abnormal findings, with STV240 values significantly below the cut-off values of the STV16. For that reason, the STV240 could not be used for the clinical decision making, as the values derived from the new algorithm were significantly lower in comparison to the ones for STV16.

This observation led to the hypothesis, that the reference values for the STV240 should be different in comparison to the existing reference values for the STV16. This hypothesis was not only based on clinical observation. The discrepancy noted between the two different algorithms is also logically sound, as it is to be expected that the variation between two subsequent beats will be notably lower as the variation between 7-10 subsequent heartbeats.

The data resulting from our single-center, non-interventional, prospective clinical study confirmed our hypothesis and allowed us to calculate the reference values for the STV240. Those reference values have been derived from a normal collective of our clinic and could therefore be eventually implemented in the antenatal monitoring of normal fetuses. However, further evaluation and validation of every new medical method are required and comparison of our data to data of other perinatal centres around the world in the future would be of great interest.

Our results are consistent with those of other study groups developing reference charts for the STV when measured with a different algorithm which also attempts to approximate the beat-to-beat variation of the FHR. In the OmniviewSisPorto 3.7 system, for instance, the STV is calculated through the difference between adjacent FHR and also results in lower normal values in comparison to the STV16 [23].

Of paramount importance for every clinician using the new algorithm in her or his everyday practice, is to know that the normal values for the STV240 (not only the mean value but also the 95th percentile) lie beneath the, up until now, established cut-off for the STV16. This stresses the fact that every clinician using computerised CTG should be, in advance, well aware of the algorithm implemented in his CTG monitors. Otherwise, there is the threat of unnecessary iatrogenic premature deliveries, with all relevant risks.

Furthermore, we were able to identify and confirm the effect of corticosteroids in the context of RDS prophylaxis on the STV of the FHR. Our results showed, in accordance to the existing literature, that the RDS-prophylaxis has a transient effect on the STV. More specifically, the intramuscular administration of corticosteroids leads to a transient increase of the STV in the first 24h, followed by a transient

decrease. The STV returns to its normal values 72h after the first intramuscular corticosteroid injection. These observations stress once again the fact that a decreased STV within the first 72h after administration of RDS prophylaxis should not be an indication for an early delivery.

Another interesting fact that occurred from our data is the correlation between STV of the FHR and week of pregnancy. It is known that in the earlier stages of pregnancy the variability of the FHR is lower, because of the immaturity of the fetal autonomous system. Our study results have demonstrated a correlation between the week of pregnancy and the STV240, failed however to confirm one between the STV16 and the week of pregnancy. It is also intriguing, that the transient changes of the STV under RDS prophylaxis are more apparent in the case of STV240 in comparison to STV16. These combined facts raise further the question, whether the STV240 can indeed better approximate the beat-to-beat variation and is thus more accurate in comparison to the STV16. This question warrants further investigation, as our study population was eventually to small to draw definite conclusions.

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RESULTING PUBLICATIONS AND ABSTRACTS

Publications in peer reviewed Journals

1. Kouskouti C, Jonas H, Regner K, Ruisinger P, Knabl J, Kainer F. Validation of a new algorithm for the short-term variation of the fetal heart rate: an antepartum prospective study. J Perinat Med. 2017 Jun. doi: 10.1515/jpm-2017-0035. [Epub ahead of print]
2. Kouskouti C, Regner K, Knabl J, Kainer F. Cardiotocography and the evolution into computerised cardiotocography in the management of intrauterine growth restriction. Arch Gynecol Obstet. 2017 Apr;295(4):811-816.

Abstracts in Congresses

1. Kouskouti C., Jonas H., Regner K., Knabl J., Kainer F. Short term variation of the fetal heart rate: normal values for 2 different computational algorithms. POSTER, 16th World Congress in Fetal Medicine, 25-29th June 2017, Ljubljana, Slovenia.
2. Kouskouti C., Regner K., Jonas H., Knabl J., Kainer F. Normwerte für zwei unterschiedliche Algorithmen für die Auswertung der Kurzzeitvariation der fetalen Herzfrequenz. POSTER, 61. Kongress der DGGG, 19-22nd October 2016, Stuttgart, Germany.
3. Kouskouti C., Regner K., Jonas H., Knabl J., Kainer F. Kurzzeitvariation der fetalen Herzfrequenz: die unterschiedlichen Algorithmen. POSTER, 90. Tagung der Bayerischen Gesellschaft für Geburtshilfe und Frauenheilkunde e.V. (BGGF), 5-7th May 2016, Nuremberg, Germany.
4. Kouskouti C., Jonas H., Regner K., Knabl J., Kainer F. Neue Methode für die Auswertung der Kurzzeitvariation der fetalen Herzfrequenz. ORAL PRESENTATION, 27. Deutscher Kongress für Perinatale Medizin, 1-3rd December 2015, Berlin, Germany.

APPENDIX A

Declaration of Conformity for the Avalon Fetal Monitors

PHILIPS

CE_{0366}

DECLARATION OF CONFORMITY

Philips Medizin Systeme
Böblingen GmbH
Hewlett-Packard Str.2
71034 Böblingen
Germany

Declares under our sole responsibility that the product:

Product Name	Avalon Fetal Monitor FM20, FM30, FM40, FM50
Product Model Number or Designator	M2702A, M2703A, M2704A, M2705A
Including the transducers:	M2734A, M2735A, M2736A
And patient module:	M2738A
Starting Revision	SW Revision F.0
Device Classification	Class IIB (Rule 10, Annex IX)
Global Medical Device Nomenclature Code (GMDN)	37796 (M2702A, M2703A, M2704A, M2705A)
	37258 (M2734A)
	36553 (M2735A, M2738A)
	32657 (M2736A)
Product Options/Accessories	All options and accessories as described in the accompanying documents

to which this Declaration relates is in conformity with the provisions of Council Directive: 93/42/EEC (Medical Devices Directive).

The Manufacturer is certified by the Notified Body listed below to EN ISO 13485 and Annex II-Section 3.2 of the Medical Device Directive. Copies of the Quality System certificates are available upon request.

Name/Address of Notified Body: VDE Testing & Certification Institute, Merianstr. 28, D-63069 Offenbach/Main, Germany

Supplementary Information:

The products listed above have been tested in a typical configuration as described in the Manufacturer's accompanying documentation, and are fully compliant with the standards listed below. Additionally the products listed above have been designed, manufactured, tested, and found to be compatible with the devices and accessories described by the manufacturer in the devices accompanying documentation:

EN 60601-1:1990 + A1:1993 + A2:1995	Medical electrical equipment – Part 1: General requirements for safety
EN 60601-1-2:2001	Medical electrical equipment – Part 1-2: General requirements for safety – Collateral standard: Electromagnetic compatibility – Requirements and tests
EN 60601-2-30:2000	Medical electrical equipment – Part 2-30: Particular requirements for the safety of automatic cycling indirect blood pressure monitoring equipment
EN 60601-2-37:2001 + A1:2004	Medical electrical equipment – Part 2-37: Particular requirements for safety of ultrasonic medical diagnostic and monitoring equipment
EN 60601-2-49:2001	Medical electrical equipment – Part 2-49: Particular requirements for the safety of multifunction patient monitoring equipment
EN 9919:2005	Medical electrical equipment: Particular requirements for the basic safety and essential performance of pulse oximeter equipment for medical use

Signature: *Peter Ohanian*

Date: 04-Dec-2008

Printed Name: Peter Ohanian
Title: Sr. Director, Quality & Regulatory

Place of Issue: Böblingen

(Form No. A-Q2920-00316-F4 Rev. D)
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APPENDIX B

Informed consent form in german (Einwilligungserklärung)

Klinik Hallerwiese · St.-Johannis-Mühlgasse 19 · 90419 Nürnberg

Patienteninformation und Einwilligungserklärung für klinische Studie

Titel der Studie: Kurzzeitvariation der fetalen Herzfrequenz in intrauteriner
                     Wachstumsretardierung

Prüfstelle: Abteilung für Geburtshilfe und Pränatalmedizin
                     Klinik Hallerwiese
                     St.-Johannis-Mühlgasse 19, 90419 Nürnberg, Tel. 0911/3340-2300

Prüfleiter: Chefarzt Professor Dr. Franz Kainer
                     Abteilung für Geburtshilfe und Pränatalmedizin
                     Klinik Hallerwiese
                     St.-Johannis-Mühlgasse 19, 90419 Nürnberg
                     Tel. 0911/33 40 - 23 00
                     Franz.Kainer@diakonieneuendettelsau.de

Prüfärzte: Assistenzärztin Christina Kouskouti
                     Assistenzärztin Dr. med. Kerstin Regner

Sehr geehrte Patientin,

wir möchten Sie fragen, ob Sie bereit sind, an der nachfolgend beschriebenen klinischen Studie teilzunehmen.

Klinische Studien sind notwendig, um Erkenntnisse über die Sicherheit, Eignung und Leistungsfähigkeit von Medizinprodukten zu gewinnen oder zu erweitern. Diese klinische Studie wird in der Abteilung für Geburtshilfe und Pränatalmedizin der Klinik Hallerwiese durchgeführt.

Ihre Teilnahme an dieser klinischen Studie ist freiwillig. Sie werden in diese Studie also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Sofern Sie nicht an der klinischen Studie teilnehmen, erwachsen Ihnen daraus keine Nachteile.

Sie wurden bereits auf die geplante Studie angesprochen. Der nachfolgende Text soll Ihnen die Ziele und den Ablauf erläutern. Anschließend wird ein Prüfarzt das Aufklärungsgespräch mit Ihnen führen. Bitte zögern Sie nicht, alle Punkte anzusprechen, die Ihnen unklar sind. Sie werden danach ausreichend Bedenkzeit erhalten, um über Ihre Teilnahme zu entscheiden.

1. Warum wird diese Studie durchgeführt?

Teil der Betreuung während der Schwangerschaft ist die Aufnahme der kindlichen Herztöne auf eine Kurve, genannt Cardiotokogram (CTG). Anhand des Musters dieser Kurve wird entschieden, ob es der Norm entspricht oder auffällig ist. Auffälligkeiten im CTG können ein Hinweis darauf sein, dass das Baby nicht mehr ausreichend versorgt ist.

Die kindlichen Herztöne werden elektronisch ausgewertet. Bislang gab es nur ein elektronisches System für die CTG-Auswertung mit Normwerten.

Durch Fortschritte in der Technologie und der EDV konnte ein neues, modernes System für die elektronische CTG-Auswertung entwickelt werden. Dieses System kann noch feinere Messungen bei der Aufzeichnung der CTG-Kurven vornehmen. Die Routine-Untersuchungen in unserer Klinik werden standardmäßig mit diesem neuen System durchgeführt. Für dieses elektronische System gibt es noch keine Normwerte.

Ziel dieser Studie ist es Normwerte für dieses neu entwickelte System zu erheben und zu vergleichen, ob das neue System dem alten überlegen ist, vor allem bei der Beurteilung von Wachstumseingeschränkten Kindern.

> **Ziel der Studie ist der Vergleich von zwei unterschiedlichen elektronischen Systemen für die CTG-Auswertung.**

2. Wie ist der Ablauf der Studie?

Wie es Ihnen bereits bekannt ist, werden im Rahmen der Betreuung bei uns täglich CTGs geschrieben, um das Wohlbefinden des ungeborenen Kindes zu überwachen. Außerdem werden Ultraschall und Doppler Untersuchungen des Babys zur Bestätigung eines normalen Wachstums, oder um sein Wachstum zu überwachen, falls Auffälligkeiten aufgetreten sind, durchgeführt.

Für diese Studie werden die CTG-Kurven, die von Ihnen routinemäßig erhoben werden, mit beiden elektronischen Systemen ausgewertet, damit neue Normwerte für das neue System erstellt werden können, um die beiden Systemen zu vergleichen. Hierfür ist Ihre Zustimmung nötig.

Zusätzlich werden die Daten von Ihren Ultraschalluntersuchungen dokumentiert, um festzustellen, ob Ihr Baby ein normales Wachstum oder eine Wachstumseinschränkung hat. Und zum Schluss werden die Geburtsdaten (z.B. Gewicht, Blutwerte, APGAR) Ihres Babys dokumentiert, um die Genauigkeit des Systems zu kontrollieren.

> **Für die Studie werden Ihre geplanten CTGs mit beiden elektronischen Systemen analysiert.**

3. **Habe ich einen persönlichen Nutzen oder Risiken mit der Teilnahme an der Studie?**

Weder einen persönlichen Nutzen, noch Risiken sind mit Teilnahme an dieser Studie verbunden.

Es werden bei Ihnen keine zusätzlichen Untersuchungen oder Interventionen durchgeführt und jede klinische Entscheidung wird anhand etablierter Verfahren getroffen.

Da es für Sie keine studienbedingten Risiken gibt, wird keine verschuldensunabhängige Versicherung im Rahmen der Studie abgeschlossen.

4. **Was geschieht mit meinen Daten?**

Ihre Daten werden in unserer Klinik, von unten genannten Mitarbeitern, aufgenommen und elektronisch gespeichert. Zu Ihren Originaldaten haben nur unten genannte Mitarbeiter Zugriff. Diese Originaldaten werden anschließend irreversibel anonymisiert und der Firma Philips Medizin Systeme Böblingen weitergegeben, welche die Auswertung der CTG-Kurven mit beiden elektronischen Systemen durchführt. Diese Auswertungen werden dann für die Ziele der Studie verwendet, um die Normwerte zu erstellen und die beiden Systeme zu vergleichen.

__Datenschutzpassus__

__Bei dieser Studie werden die Vorschriften über die ärztliche Schweigepflicht und den Datenschutz eingehalten. Es werden persönliche Daten und Befunde über Sie erhoben, gespeichert und in irreversibel anonymisierter Form weitergegeben.__

__Der Zugang zu den Originaldaten ist auf folgende Personen beschränkt:__
__Chefarzt Professor Dr. F. Kainer__
__Assistenzärztin C. Kouskouti__
__Assistenzärztin Dr. med. K. Regner__
__Hebamme H. Jonas__
__Die Unterlagen werden in der Abteilung für Geburtshilfe und Pränatalmedizin der Klinik Hallerwiese elektronisch und mit Passwort geschützt aufbewahrt.__
__Im Falle des Widerrufs Ihrer Einwilligung werden die gespeicherten Daten vernichtet.__

__Im Falle von Veröffentlichungen der Studienergebnisse bleibt die Vertraulichkeit der persönlichen Daten gewährleistet.__

DIAKONIE NEUENDETTELSAU
Klinik Hallerwiese
Abteilung für Geburtshilfe und Pränatalmedizin
Chefarzt Prof. Dr. F. Kainer

LEBEN
GESTALTEN

Klinik Hallerwiese · St.-Johannis-Mühlgasse 19 · 90419 Nürnberg

Kurzzeitvariation der fetalen Herzfrequenz in intrauteriner Wachtumsretardierung

Einwilligungserklärung

Ich bin in einem persönlichen Gespräch durch den Prüfarzt ausführlich und verständlich über die klinische Studie aufgeklärt worden. Ich habe darüber hinaus den Text der Patienteninformation sowie die hier nachfolgend abgedruckte Datenschutzerklärung gelesen und verstanden. Ich hatte die Gelegenheit, mit dem Prüfarzt über die Durchführung der klinischen Studie zu sprechen. Alle meine Fragen wurden zufrieden stellend beantwortet.

Mir ist bekannt, dass ich jederzeit und ohne Angabe von Gründen meine Einwilligung zur Teilnahme an der Studie zurückziehen kann (mündlich oder schriftlich), ohne dass mir daraus Nachteile für meine medizinische Behandlung entstehen.

Ich erkläre mich bereit, an der oben genannten klinischen Studie freiwillig teilzunehmen.

Ich bin mit der Erhebung und Verwendung persönlicher Daten und Befunddaten nach Maßgabe der Patienteninformation einverstanden.

Die Patienteninformation sowie eine Kopie der Einwilligungserklärung habe ich erhalten.

_____   _____
Name der Patientin in Druckbuchstaben   geb. am

_____   _____
Unterschrift der Patientin   Ort, Datum

Ich habe das Aufklärungsgespräch geführt und die Einwilligung der Patientin eingeholt.

_____
Name des Prüfarztes/der Prüfärztin in Druckbuchstaben

_____   _____
Unterschrift des aufklärenden Prüfarztes/der Prüfärztin   Ort, Datum

55

Eidesstattliche Versicherung

Kouskouti, Christina

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Short Term Fetal Heart Rate Variation in Intrauterine Growth Restriction: development of reference values for a new computational algorithm
(Kurzzeitvariation der fetalen Herzfrequenz in intrauteriner Wachstumsretardierung: Erstellung von Normkurven für einen neuen Berechnungsalgorithmus)

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Nürnberg, 10.07.2017

Ort, Datum

Christina Kouskouti

Unterschrift Doktorandin/Doktorand