

DESCRIPTION OF FETAL HEART RATE PATTERNS AT 20 TO 24 WEEKS GESTATION

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**Thesis submitted as partial prerequisite for the degree Masters in Medicine at
the Tygerberg campus, Department of Obstetrics and Gynaecology**

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and that I have not previously in its entirety or in part, submitted it at any university for a degree.

Signature

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Name in full

29 March 2012

Date

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Acknowledgements

I would like to thank Prof Hein (HJ) Odendaal as principal promoter for his constant enthusiasm and encouragement throughout this project. His knowledge and wisdom has led me to a greater appreciation of and excitement for the world of research.

Also, Coen (CA) Groenewald from the University of Stellenbosch Department of Obstetrics and Gynaecology as well as Michael (MM) Myers and Bill (WP) Fifer from the Departments of Psychiatry and Pediatrics, Columbia University, New York City who assisted greatly in planning and executing this project.

Other contributors from the PASS Network, Gary (GDV) Hankins from the Department of Obstetrics and Gynecology, University of Texas Medical Branch: Galveston, Texas and Caroline Signore of the Eunice Kennedy Shriver National Institute of Child Health and Human Development for the opportunity to conduct this sub-project under the constant support and input from the Safe Passage Study group.

A special mention must also go to Prof Daan (DG) Nel from Department of Statistics and Actuarial Science, Stellenbosch University, for his assistance during data conversion and analysis.

Thank you to the Department of Obstetrics and Gynaecology Tygerberg Hospital for the opportunity to search and study deeper into the beautiful and miraculous field of Obstetrics.

And most importantly, to my husband, Ross, for his support and love through this process, thank you.

Abstract

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Introduction

Accurate computerized analysis of the fetal heart rate (FHR) pattern has become more feasible and clinically relevant in recent years. Taking into account advances in neonatal care resulting in a declining lower limit for fetal viability as well as research into fetal effects of maternal high risk behaviour and escalating intra-uterine exposure to harmful toxins and drugs, fetal heart rate patterns need to be more accurately described in earlier gestations than what is currently available in literature. With advancing technology it is becoming possible to accurately record and interpret the FHR patterns from gestations as early as 20 weeks' gestation. By using the Monica AN24 transabdominal electrocardiographic fetal monitor and product specific software, we analysed early FHR patterns according to the Dawes-Redman criteria, as used in later gestations.

Methods

The aim of our study was to describe patterns of FHR (short-term variability, basal heart rate, accelerations and decelerations) at 20-24 weeks' gestation. Physiological data were obtained from the routine second trimester fetal assessment by the Monica AN24 monitor as used in the Safe Passage Study. As of December 31, 2009, 411 participants completed their first fetal assessment and met our inclusion criteria. Because our aim was the description of patterns in pregnancies with a normal outcome, we excluded all adverse neonatal outcomes, preterm deliveries, babies with low birth weights as well as cases where delivery data were lost. After recordings of poor technical quality were also removed from our data pool, 281 recordings remained for analysis.

Results

Distinct FHR patterns and quantifiable parameters of heart rate variability were consistently observed. In contrast to what has previously been published, accelerations of the FHR and reassuring baseline variation are present from as early as 20 weeks.

Conclusion

Information from this study provides an important foundation for further studies of early FHR patterns and it will help us better assess the fetus at a crucial age for indicators of good outcome at early delivery.

Opsomming

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Promotor:	Prof HJ Odendaal
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Data analiese:	Prof DG Nel

Inleiding

Akkurate gerekenariseerde ontleding van die fetale hartpatroon het in die afgelope paar jaar meer tegnologies haalbaar met toenemende kliniese toepassing geword. Tans ervaar ons besondere vooruitgang in neonatale sorg en dus dalende grense vir vroeë lewensvatbaarheid in kliniese praktyk. Daar is ook 'n toename in navorsing oor moederlike hoë risiko gedrag tydens swangerskap en die effek hiervan op die ontwikkeling die fetus asook die neonatale uitkomst. Akkurater beskrywing van fetale hartpatrone in vroeë gestasies as wat huidiglik in die literatuur beskikbaar is, is dus genoodsaak om die effekte van blootstelling op die fetus waar te neem. Met vooruitgang in tegnologie is dit nou moontlik om deur nie-indringende elektrokardiografie, fetale hartpatrone te registreer en te interpreteer van so vroeg as 'n swangerskapsduurte van 20 weke. Deur die gebruik van die Monica AN24 transabdominale monitor en produk-spesifieke programmatuur, kon ons vroeë fetale hartpatrone ontleed volgens die Dawes-Redman kriteria wat gewoonlik in later swangerskapsduurtes gebruik word.

Metodes

Die doel van ons studie was die beskrywing van verskeie fetale hartpatrone (naamlik korttermyn variasie, basale hartspoed, versnellings asook vestadigings) rondom 20 – 24 weke swangerskapsduurte.

Fisiologiese data is in die tweede trimester verkry deur die Monica AN24 monitor, soos gebruik word in die voortgaande Veilige Geboorte Studie by Tygerberg hospitaal. Tot en met 31 Desember 2009, het 411 deelnemers hulle eerste fetale evaluasie vir die Veilige Geboorte Studie gehad en ook voldoen aan die insluitingskriteria van hierdie projek.

Aangesien ons fokus die beskrywing van hartpatrone in normale swangerskappe was, het ons alle nie-wenslike neonatale uitkomst, voortydse verlossings, babas met lae geboorte gewig asook gevalle waarvan die geboortedata nie beskikbaar was nie, uitgesluit. Alle

opnames met sub-standaard tegniese kwaliteit is ook verwyder uit ons finale data vir ontleding, wat ons met 281 opnames gelaat het vir hierdie studie.

Resultate

Duidelike fetale hartpatrone en meetbare afmetings is deurgangs opgemerk. In teenstryd met wat voorheen gedokumenteer is, is die teenwoordigheid van versnellings asook gerusstellende basislyn variasie meetbaar vanaf 20 weke gestasie.

Samevatting

Informasie vanaf hierdie studie verskaf 'n belangrike grondslag vir verdere projekte in die ontleding van fetale hartpatrone met die fokus op ondersoek van vroeë voorspelling van goeie neonatale uitkomst.

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Introduction

Electronic fetal heart rate (FHR) monitoring is widely used to evaluate fetal well-being once the fetus has become viable. Since the introduction of FHR monitoring, advanced software has been developed for computerized analysis to improve the accuracy of interpretation of FHR patterns before and during labour. ^(1,2)

Neonatal intensive care has become very sophisticated since the introduction of FHR monitoring, with improving survival rates of extremely premature infants. Limits for fetal viability are often pushed forward to 24 weeks and even earlier. ⁽³⁾ Earlier viability necessitates monitoring of the FHR in high-risk pregnancies, from early gestations, to prevent demise or severe neonatal asphyxia before delivery.

Very little has been published on the interpretation of FHR patterns before 26 weeks. It is therefore difficult to know how to accurately interpret FHR patterns in early pregnancy as most of the research has been done in more advanced gestations. As it has been presumed that maturation of the autonomic nervous system (which is closely associated with changes in the fetal heart rate patterns) and the development of the fetal cardio-regulatory mechanism occur at/after 30 weeks' gestation, there is less certainty about fetal heart rate patterns before this gestation. ⁽⁴⁾ In addition, as research on fetal behaviour and maternal exposure is increasing, it is essential that we develop in-depth knowledge of FHR patterns in the normal fetus in very early gestations, even before the present age of fetal viability.

Another reason for the lack of knowledge about early FHR patterns based on real beat-to-beat changes, as obtained through true R-wave intervals in fetal electrocardiography (fECG), is due to the limitations of using fetal scalp electrodes. These can only be used during labour after membranes have been ruptured and seldom in the extremely premature fetus. The danger of HIV transmission by scalp electrodes is also a relevant concern. Furthermore, fetal heart rate pattern interpretation from ultrasound/Doppler studies is based on the implementation of averaging techniques and therefore not as accurate as fECG. ⁽⁵⁾ For these obvious reasons the terminology on cardiotocography as recommended by the National Institute of Child health and Human Development (NICHD) is limited to term and near-term fetuses. ⁽⁶⁾

As mentioned above, fECG is superior to Doppler ultrasound in evaluating fetal cardiac rhythms and rates as it produces higher quality recordings (even in very early gestations) through true beat-to-beat variation (measuring R-wave intervals) in contrast to an averaged

heart rate. ^(2, 7, 8) Unfortunately, non-invasive fECG monitoring devices have been lacking in technological accuracy in the past, but through using the Monica AN24 electronic fetal monitoring device it has now been shown that more than 80% of antenatal recordings are of good quality and, more importantly, correlation with the scalp electrode regarding the FHR and variation is excellent. ⁽⁹⁾

As the characteristics of the FHR pattern in early pregnancy are undetermined, we proceeded to describe the FHR patterns between 20-24 weeks' gestation in 281 uncomplicated pregnancies with live, term deliveries and good perinatal outcomes.

Literature Review

Since its first publication in 1997, the criteria and terminology recommended by the "National Institute of Child health and Human Development (NICHD) Research Planning Workshop" to evaluate fetal cardiotocography (CTG) have been used clinically, and in research, in term and near-term fetuses. ⁽⁶⁾ However, the NICHD Workshop Criteria applies to term and near-term fetuses and have not been investigated in terms of relevance for pre-viable gestations.

In our preliminary literature review we found very little published data on the interpretation of FHR patterns before 26 weeks' gestation. This is probably due to the limitations mentioned above in obtaining accurate recordings in these pre-viable fetuses. The technology for reliable fECG monitoring has largely been unavailable up to now. ⁽¹⁰⁾ De Vries *et al.* described diurnal changes in basal fetal heart rate as well as variation from 20 weeks gestation, resembling that of the term fetus, with decelerations more frequent than accelerations although diurnal changes in accelerations and decelerations were small. ⁽¹¹⁾ However, the publications available on FHR patterns before 26 weeks gestation present few findings regarding the expected baseline short term variation in these early gestation fetuses. Based on the limited data available, these studies generally conclude that fetuses less than 26 weeks show reduced baseline variability as well as diminished acceleratory response to maternal/additional stimuli in comparison to term fetuses. These studies also suggest that there are usually more decelerations than accelerations in early gestations. ^(4, 11-14)

Preliminary Study

Through the ongoing Safe Passage study at Tygerberg hospital, data were obtained from 74 fetuses between 20 and 24 weeks gestation during November and December 2009, using the Monica AN24 device. The mean success rate of extracting fECG from these recordings was 94.8% (SD +15.1). Sixty eight (91.9%) of the recordings were > 85% successful and 64 (86.4%) were > 90% successful. There were only 3 recordings less than 75% successful, i.e. 74.5%, 8.74% and 11.96%. It is uncertain why the success rates in the last two subjects were so poor. The success rate for the Monica device is derived by proprietary software (the DK program) and in rare instances can be negatively influenced by many factors including poor electrode contact, poor application of the Monica device, patient movement or even fetal factors. Considering this was the first time this device was used in South Africa, there might also have been an operator dependant factor even though it is not a difficult product to set up and the operators have become very skilled in acquiring good quality data. As the product analysing and extracting software is constantly updated and improved by the manufacturer (with regular feedback from the PASS network project managers), we anticipated even higher success rates for data-extraction in follow-up projects.

Study Aims

The aim of our study was to describe fetal heart rate patterns at 20 to 24 weeks gestation using the high resolution ECG data available from the Monica AN24 monitor through the ongoing Safe Passage study at Tygerberg Hospital. We wanted to specifically look at the acceptable range for baseline variability in these early gestations, as well as describe our findings regarding basal heart rate, accelerations and decelerations. Our primary goal was to use the Dawes-Redman criteria (usually implemented for analysis at term or near-term gestations) to characterize FHR patterns at 20 weeks to 23 weeks 6 days gestation, limiting our evaluation to fetuses with good perinatal outcomes. ⁽⁶⁾

We initially anticipated the inclusion of 400 participants in this descriptive analysis, but were aware that our final numbers for analysis would depend on the application of very strict exclusion criteria in order to limit our study to uncomplicated pregnancies as far as possible, measured against good fetal outcome. It was planned from the beginning of this project to include all available data up to Dec 31, 2009 (with data collection using the Monica AN24 starting in October 2008).

Although the PASS Network's research (from which our study data were obtained) aims at identifying the relationship between alcohol and smoking and poor perinatal outcome, no hypotheses related to alcohol or nicotine exposure were proposed and our data collection for this specific sub-project was blinded to the presence of these factors.

However, we believed that through focussing on normal pregnancies as far as possible and adhering to very strict exclusion criteria this project would provide essential normative values for future studies, in particular the effects of maternal high risk behaviour on FHR patterns as controlled by the autonomic nervous system from early gestation.

Methods

PASS Network & Safe Passage Study

The PASS network consists of a multicentre, international group of doctors, midwives, researchers and statisticians who primarily investigate the role of prenatal alcohol exposure in the risk for Sudden Infant Death Syndrome and adverse pregnancy outcomes, such as Stillbirth and Fetal Alcohol Spectrum Disorders (see www.safepassagestudy.org).

The Safe Passage Study is the Main Study run by the PASS Network through which a planned 12 000 women from South Africa and the United States will be enrolled and followed through pregnancy as well as the first year of life. Meticulous data collection at multiple visits assisted greatly in acquiring accurate data for extensive analysis relevant to our project.

Initial recruitment and assessment is done at the Bishop Lavis antenatal site, but all participants are scheduled to be evaluated at the Tygerberg Hospital PASS unit between 20 – 24 weeks gestation (the so-called “F1 visit”) at which time a fetal and maternal ECG recording is made using the Monica AN24 monitor amongst other data collection. At recruitment for Safe Passage Study, all women have an ultrasound examination done by a qualified sonographer to determine gestational age as accurately as possible. Written informed consent to record the FHR is part of the consent for the main study.

No data in addition to what has been ethically approved and collected through the Safe Passage Study were used for this specific project (Ethics approval number: N06/10/210)

Although this population was specifically chosen based on the high incidence of maternal alcohol exposure and the main aim of the PASS network is the investigation of maternal high risk behaviour and the association with adverse pregnancy outcomes, no hypotheses related to maternal alcohol ingestion or smoking were proposed for this particular sub-project. Through focussing on uncomplicated pregnancies and excluding all adverse perinatal outcomes we postulated a study population representative of the larger South African community.

Monica AN24 monitor

The Monica AN24 is a small, wireless, electronic fetal monitoring device that is connected to the gravid abdomen by 5 high quality electrocardiogram electrodes. Four electrodes are placed in a diamond-shaped pattern, one just below the umbilicus, one just above the pubic hairline, and the other two laterally, equal distances from the top and bottom ones. The fifth electrode, for reference, is placed just lateral to the one on the right side.

Figure 1: Monica AN24

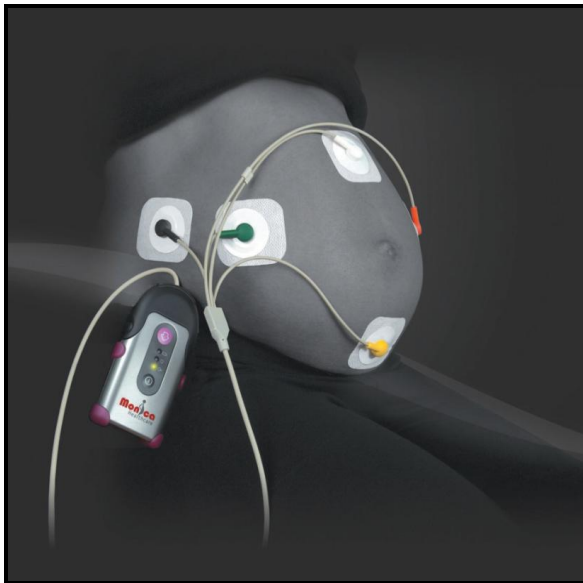
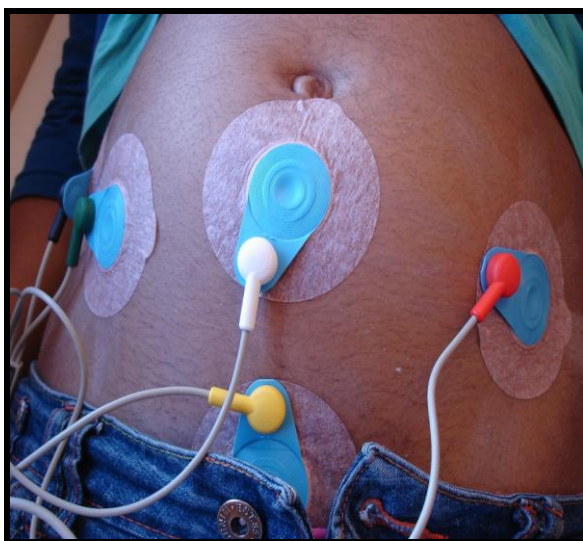


Figure 2: Monica AN24 at 20 weeks and 4 days gestation



Recordings of the FHR are done in quiet rooms equipped for use by the study. Participants lie in a 15° right or left lateral position, with a wedge placed under one of the buttocks to prevent supine hypotension. Before application the skin is lightly braised to remove superficial dry squamous cells, which is essential to obtain low impedance. The skin is also washed with soap and water if the participant has used any skin ointment. After application the 5 electrodes are connected to the monitoring device which is attached to the abdominal wall with an elastic band to prevent it from falling down and to keep all the devices in similar positions. At the end of the recording, of at least 30 minutes, the device is removed and connected to a laptop for downloading of the raw data using the DK 1.4a software as developed by the manufacturers. Recordings of the FHR can't be seen by the person doing the recording and both participant and operator are kept blind from the results of all analyses.

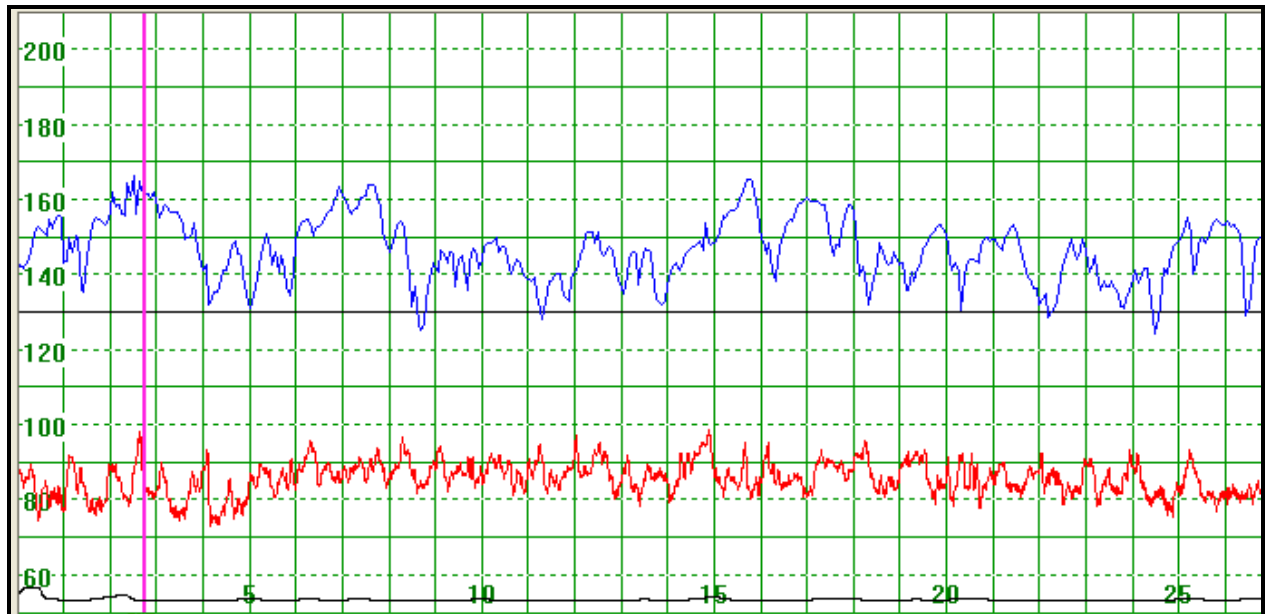
Monica amplifies ECG signals that pass through the abdominal wall to determine the maternal and fetal heart rates (4 leads represented by four colours in this picture):

Figure 3: Maternal and fetal QRS complexes



After recording, the device is connected to a designated laptop computer through which product specific software analyses and extracts the raw data:

Figure 4: Data after extraction



This is what the recording would look like after extraction of the raw data was done in a 20 week fetus with fetal cardiocograph on the top (blue), followed by maternal heart rate (red) and then myometrial activity in the uterine wall (black).

The program also reports on other observations (maternal movements and activities) during the recording as well as loss of contact of an electrode through a coded warning system that is marked on each recording at the time of the incident.

Only recordings with a minimum of 30 minutes fetal ECG tracing and with no more than 49% data loss would be included in this project. Data loss of 50 % or more per recording was automatically flagged by the program software and these recordings were excluded from our final data pool.

No upper limit was set to recording time and analysis was done per recording in its entirety (ranging between 30 and 96 minutes with a mean of 46.4 min and a median of 44 min). Specific findings were later standardized to 10 minute intervals for future comparison between different subgroups within our study population.

Data Collection and analysis

The first 411 recordings (total duration 18,385 minutes) done between 20-24 weeks (more precisely 140 to 167 days), collected from 1 October 2008 to 31 December 2009, were used for this study. Recordings were done by PASS network staff as part of standard data collection for the Safe Passage Study. The Dawes and Redman criteria (also incorporated in the Oxford System for Computer analysis) of the DK 1.4a programme were used for analyses of the raw data. ⁽⁵⁾ As the duration of the recordings differed, the number of accelerations and decelerations were also expressed per 10 minutes of recording. These findings were then entered on an Excel spread sheet in addition to gestational age at the time of recording as well as delivery data (including delivery gestation, birth weight, sex, apgar scores and fetal or neonatal outcomes).

Due to the pre-viable nature of these fetuses (according to our institution's limits of fetal viability set at 27 weeks sure gestation, as reflected in TBH "Preterm labour" and "Preterm prelabour rupture of membranes" protocols) and also the fact that normal parameters have not been set for these very early gestation fetal heart rate recordings, all participants (as well as the Monica-operator) were blinded to the actual data recording at the time of data collection. Only after the recording was completed and the participant had finished all other data collection, would the operator connect the Monica AN24 to a designated laptop for data download. Even at the time of download the data was still in an unreadable state and would only be extracted and analysed later by a medical professional and stored for further analysis.

Information regarding the precise gestation at the time of data recording as well as delivery was obtained from maternal records at the Research Unit and manually added to the analysed data in Excel.

With the Monica AN24 being a relatively new product, the software is still regularly updated by the manufacturer. For this project, initial analyses as well as conversion from primary ("raw") recordings to extracted data (Figure 3 & Figure 4 above) were done using one of the first analysis programs, Monika DK1.4a, with pre-programmed Dawes-Redman Criteria (the parameters of which are summarised in **Error! Reference source not found.** later).

Through the help of Prof DG Nel from Department of Statistics and Actuarial Science, Stellenbosch University, we analysed our Excel findings with histograms looking at frequency, distribution, means and medians.

Inclusion and Exclusion Criteria for initial enrolment

Bishop Lavis Antenatal Clinic has been selected as an approved site for recruiting participants in the Safe Passage Study through the PASS Network. All pregnant women who attend this facility (and who qualify according to the outlined requirements) are offered the opportunity to participate in this study after proper counselling has been provided and informed consent given.

Inclusion Criteria

1. Able to provide informed consent.
2. Pregnant female of any race or ethnicity, carrying one fetus during pregnancy.
3. Age 16 years or older, inclusive at time of consent.
4. Must speak English or Afrikaans (exclusively Xhosa and Somali speaking persons will be excluded, which is less than 5% of the population).
5. At the time of recruitment visit, participant is at least 6 weeks, 0 days and less than 20 weeks, 1 day gestation,

OR

Participant is more than 20 weeks, 1 day gestation but has not had more than two prenatal visits.

AND

The current visit is not the delivery admission.

Exclusion Criteria

1. Women carrying multiple pregnancies.
2. Planned abortion
3. Moving out of catchment area prior to estimated date of delivery.
4. Unable to provide informed consent.
5. Health care provider advises against participation.

Exclusion Process

As mentioned before, through focussing on normal pregnancy outcomes we aimed at identifying normal baseline criteria for the analysis of FHR patterns in 20-24 weeks gestation fetuses. Especially with our study population being identified as a high risk population in regards to ongoing investigation of the high incidence of intra-uterine fetal demise (IUFD)/Stillbirths and Sudden infant death syndrome (SIDS) in relation to fetal exposure of alcohol and smoking.

This refining of data is reflected in Table 1.

Table 1: Exclusion process

	Total per group	% of initial participants	Participants for analysis:
Enrolled by 31 Dec 2009	411		411
Poor technical quality (Data loss >50%)	21	5.1	390
Recordings <30 min	23	5.6	371
Delivery data not available (including 2 withdrawals)	11	2.7	361
Preterm delivery (PTL) (< 259 days)	55	13.4	317
Low birth weight (< 2500 g and not PTL)	22	5.3	296
Intra-uterine death	11	2.7	295
Early neonatal death	2	0.5	294
Low birth weight according to population specific curves	39	9.5	281

Some of the recordings met more than one exclusion criteria and may have been eliminated earlier in the process which is shown in the final count after application of each individual criterion.

In order to limit the recordings to that of fetuses with good perinatal outcome, recordings of pregnancies that ended in stillbirths (2.7%) or neonatal deaths (0.5%) were excluded as well as cases where the fetus weighed less than 2,500 g (5.3%), were born before 259 days (13.4%) or weighed less than the 10th percentile on the Tygerberg growth curves (9.5%).⁽¹⁵⁾

Cases where the delivery data were not available were also excluded (some participants delivered in other hospitals) as well as recordings with durations of less than 30 minutes or where the analysis indicated that more than 50 % of the data were lost.

Through the elimination process itself we noted a few interesting findings, for example the high incidence of Preterm delivery in this population (13.4%). This finding will be discussed in detail under “Results – Preterm labour”.

Technical Quality

The technical quality of our recordings was determined by two exclusion criteria; data loss more than 50% and recording time less than 30 minutes.

Based on a publication by Graatsma *et al.* we anticipated data loss more than 50% per recording in about 20% of our participants, but were pleasantly surprised to have a recording success rate of 94.9% with only 21 recordings reflecting more than 50% data loss, a remarkably positive finding in studying these very early gestational recordings.⁽⁹⁾

Loss to follow up

Only two participants withdrew from the study (0.48%) due to personal reasons and 9 participants (2.2%) had incomplete delivery data at the time of final data capturing and were therefore also removed from the data pool for final analysis because we could not validate good perinatal outcome. That is a total of 11 participants (2.7%) that were excluded on the basis of inadequate/incomplete data capturing.

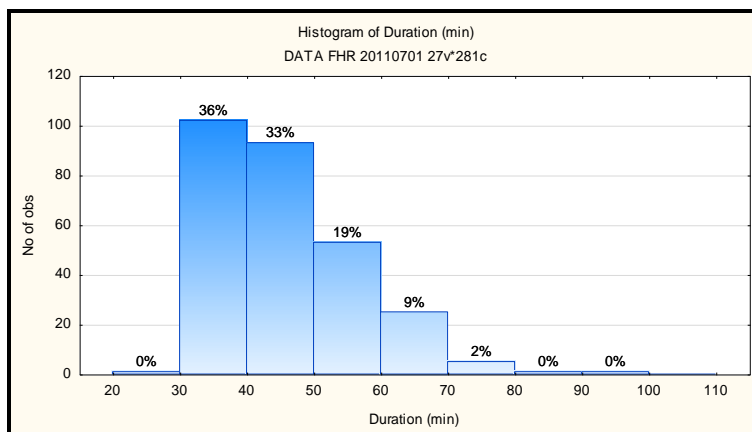
Delivery data

Adverse neonatal outcomes were the final group of eliminations and by working through all delivery data (a total of 361 recordings by this stage in the process) we had 55 participants with preterm delivery (13.4%), 22 low birth weight babies (5.4%, NOT overlapping with preterm delivery numbers). This percentage was expected, knowing that the incidence of low birth weight infants in Sub-Saharan Africa is estimated by UNICEF to be around 10% and only half of all low birth weight infants are born prematurely. ⁽¹⁶⁾ Eleven intra-uterine deaths (2.7%) and 2 early neonatal demises (0.48%) were also excluded. In addition to the standard definition of low birth weight deliveries (birth weight less than 2500g) we also cross-referenced all delivery data with population specific growth curves and excluded an additional 5 (1.2%) low birth weight babies from our final data pool before analysis. ⁽¹⁵⁾

Duration of recordings

As mentioned under “Exclusion process”, 23 recordings were eliminated before data analysis due to lack of adequate recording time. Recording time of analysed participants ranged between 30 and 96 minutes with a mean duration of 46 minutes.

Figure 5: Duration of analysed recordings



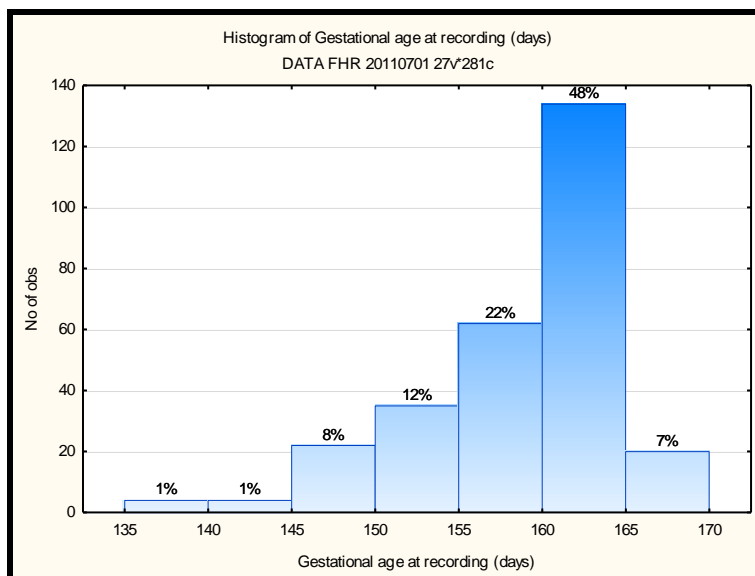
The limit of 30 minutes minimum recording time (as set in our protocol) was based on three reasons:

1. The Monika AN24 program specific software, DK 1.4a, divided each recording into 15 minute epochs and analysed all recordings over a pre-set minimum time-frame of 30 minutes. Therefore, all recordings shorter than 30 minutes would give inaccurate data after standardization of data is done by reverting back to 10 minute intervals. Also, our findings regarding frequency of occurrences would be inaccurate.
2. Although cycling between active and quiet sleep in term fetuses occurs on average every 40 minutes, we are uncertain of the time frame applicable to fetuses before 26 weeks gestation. We do however know that the presence of adequate FHR variation is reassuring irrespective of the duration of the recording as will be discussed later in this document. ⁽⁵⁾
3. Also, taking into account the practical limitations of out-patient data recording time, we decided on setting our minimum recording time at 30 minutes as this was the aimed time per recording as set by PASS Network protocol even before our project protocol was conceived.

Gestational age at recording

At recruitment for PASS Study, all women have an ultrasound (U/S) examination done by a qualified sonographer to determine the exact gestational age. For this specific study all FHR recordings were done on confirmed, sure gestations between 140 and 167 days which is between 20 weeks 0 days and 23 weeks and 6 days.

Figure 6: Gestational age at the time of recording



As you will notice, most data were incidentally collected towards the later spectrum of these parameters (23 weeks or around 160 days).

On initial planning of this project, we considered subdividing our final analysis into weekly intervals and comparing FHR parameters between each gestational week. Unfortunately, as the data analysis progressed we noticed an uneven distribution in gestational age at the time of recordings and we decided that our numbers in each gestational week did not allow for an accurate comparison. This is definitely an area for further study through using the follow up data in a validation study, which would certainly provide larger numbers and a more even distribution.

Table 2: Gestation in weeks and days

<u>Gestation in weeks:</u>	<u>Gestation in days:</u>
20 weeks	140 days
21 weeks	147 days
22 weeks	154 days
23 weeks	161 days
24 weeks	168 days
37 weeks	259 days
38 weeks	266 days
39 weeks	273 days
40 weeks	280 days
41 weeks	287 days
42 weeks	294 days
43 weeks	301 days

Recording quality and signal processing

This refers specifically to signal loss and not to other data loss as specified under the exclusion criteria and exclusion process.

In contrast to previously published results, FHR recordings with the Monica device at the 20-24 week visit of Safe Passage Study participants at Tygerberg Hospital were of high quality and remarkable detail (as discussed under preliminary study earlier) and indicate greater complexity in patterns at this age than previously appreciated. This newly acquired data suggested that the previously accepted low levels of FHR variability and lack of acceleratory response in these pre-viable fetuses were influenced by technological limitations of monitoring techniques rather than fetal prematurity alone.

All recordings with signal loss of 50% or more, irrespective of the hypothesised reason therefore, were excluded from our data pool before analysis. These parameters were decided upon based on the program specific analysis criteria through the pre-programmed Dawes-Redman analysis tool, which promptly reported data sets that were inadequate for analysis due to signal loss of more than 50%.

A total of 21 recordings were excluded after final data collection (5.1% of original 411 recordings) based on poor technical quality. This showed our recording success rate, at 94.9%, to be better than anticipated when compared to a recent publication by Graatsma *et al.* using the Monica AN24 for fetal electrocardiogram recordings between 20 to 40 weeks gestation with their success rate estimated at 82% based on signal quality alone. ⁽⁹⁾

Two of these excluded recordings resulted in early intra-uterine fetal demises. The first participant delivered a macerated stillborn baby (MSB) at 168 days gestation with the baby probably already demised at the time of recording four days earlier (at 164 days gestation) and the second stillborn baby was delivered at 236 days gestation with no detectable correlation to the poor technical quality recording at 159 days. The percentage signal loss of the 19 other excluded recordings ranged between 50.8 and 93 percent.

Of the final 281 analysed recordings, the mean percentage signal loss was calculated as 3.98%, and the maximum loss of a single recording was 46.3%.

Results

The demographic information on our study population has been summarised in Table 3 and a complete summary of the analyses is given in **Error! Reference source not found.**

Table 3: Demographics of study population

	n	%	Mean (sd)	Median	Range
Maternal Age (Years)	281	100	25.1 (5.9)	24	16 - 41
Participant Ethnicity					
Cape Coloured	280	99.6			
Other	1	0.4			
Married or Partnered	259	93.5			
High school education	72	25.6			
Height (in)	275	97.9	62.4 (2.5)	62.2	56.6 - 71.1
Height (m)	275	97.9	1.58 (2.5)	1.58	1.4 - 1.8
Pre-pregnancy weight (lbs)	138	49.1	133.1 (35.1)	123.5	70.5 - 233.7
Pre-pregnancy weight (kg)	138	49.1	60.4 (35.1)	56	32.0 - 106.0
Pre-pregnancy BMI	137	48.7	24.0 (6.2)	22.9	13.4 - 45.5

The majority of our study population is of Cape Coloured ancestry (99.6%) and maternal ages ranged from 16 to 41 years with a median age of 24. Pre-pregnancy Body Mass Index was exceptionally diverse, ranging from 13.4 to 45.5 with a median of 22.9.

A total of 281 records were included in the final analyses (13 028 minutes). For these recordings, the mean percentage signal loss was 4%.

Our final recordings reflected a 94.9% success rate in recording the FHR from maternal abdominal wall ECG electrodes using the Monica AN24 system with success defined as recordings with less than 50% data loss.

The duration of recordings ranged from 30 to 96 minutes, gestational ages at time of the recording ranging from 140 to 167 days and delivery from 259 to 296 days. Birth weights ranged from 2 520 g to 4 400 g. Basal heart rates ranged from 132 to 171 (bpm) as also illustrated in **Error! Reference source not found.**

We found that 71% of fetal heart rate recordings showed accelerations, and that decelerations were present in 67% of recordings. The mean short-term variation was 6.2msec (SD 1.4msec) which ranged from 3.2 to 12.7msec and the median of the mean minute range was 32 msec.

Table 4: Summary of Analyses

Variable	Valid N	Mean	Confidence (-95%)	Confidence (95%)	Median	Minimum	Maximum	Std. Dev.
Duration (min of recording)	281	46.4	45.4	47.6	44.0	30.0	96.0	10.7
Gestational age at recording (days)	281	159.0	158.3	159.7	161.0	140.0	167.0	5.8
Loss (%)	281	4.0	3.1	4.9	0.2	0.0	46.3	7.9
Mean bpm	281	148.0	147.3	148.6	148.1	133.8	167.8	5.4
Basal bpm	281	148.0	147.3	148.6	148.0	132.0	171.0	5.8
SA/10min	281	0.5	0.4	0.6	0.3	0.0	3.0	0.5
LA/10min	281	0.1	0.1	0.2	0.0	0.0	1.5	0.2
SD/10min	281	0.3	0.3	0.3	0.2	0.0	1.6	0.3
LD/10min	281	0.008	0.003	0.013	0.0	0.0	0.3	0.04
STV (msec)	281	6.2	6.1	6.4	6.1	3.2	12.7	1.4
MMR (msec)	281	35.1	34.3	36.0	34.6	17.5	56.8	7.1
High variation (%)	281	22.6	20.0	25.1	16.7	0.0	94.9	21.6
High variation (ms)	281	32.6	30.0	35.2	42.9	0.0	109.8	22.1
Low variation (%)	281	22.6	19.7	25.5	15.0	0.0	100.0	24.7
Low variation (msec)	281	15.7	14.3	17.0	21.4	0.0	39.0	11.7
Delivery gestation (days)	281	276.9	276.0	277.9	277.0	259.0	296.0	7.8
Birth weight (g)	281	3168	3122.3	3213.6	3120	2520	4400	388.7
Apgar score 1 min	274	8.8	8.7	8.9	9.0	1.0	10.0	0.9
Apgar score 5 min	274	9.9	9.8	9.9	10.0	7.0	10.0	0.4

BPM = Beats per minute; SA = Short accelerations; LA = Long accelerations; SD = Short decelerations; LD = Long decelerations;

STV = Short term variation; MMR = Mean minute range

Discussion

Mean and basal beats per minute

Figure 7: Mean beats per minute

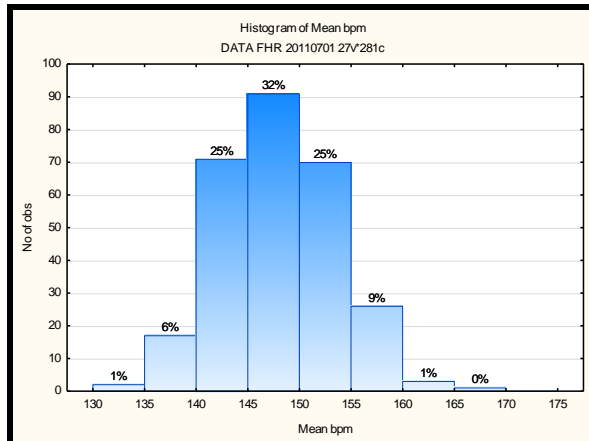
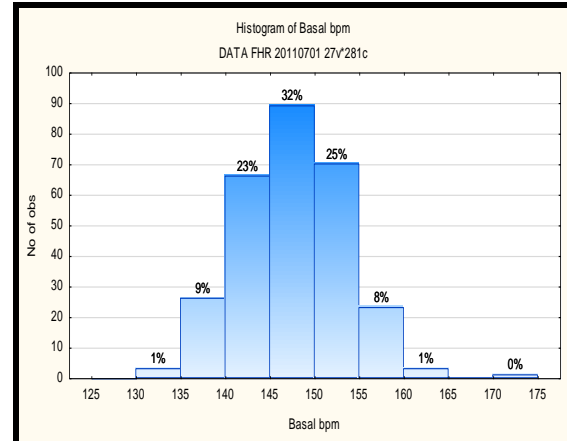


Figure 8: Basal beat per minute



The accepted range for term fetal heart rate is 110-160 bpm. ⁽⁶⁾ It is also well documented that normal fetal heart rate shows a gradual decrease up to 30 weeks gestation with basal fetal heart rate significantly higher at 20 weeks compared to later gestations. ⁽¹⁷⁾

Visser et al. made us aware of a gradual fall in basal heart rate between 24 and 30 weeks gestation (documented in their study as decreasing from 148 bpm to 140 bpm basal heart rate) where-after the heart rate remained fairly constant as we see at term. ⁽¹⁸⁾ With the accurate recordings now available from the Monica AN24 monitor, we were hoping to compare the basal heart rate between individual gestational weeks from 20 – 24 weeks gestation. Unfortunately (as mentioned earlier) due to an uneven distribution of data with most of our data collected at 23 weeks gestation, this was not possible. We do however anticipate that a follow up study will provide greater numbers and this analysis would then make it possible to investigate the possible progressive fall in basal fetal heart rate from 20 weeks gestation, in weekly intervals.

We found that FHR, as recorded from maternal transabdominal ECG electrodes, can be accurately recorded as early as 20 weeks' gestation. In contrast to what has previously been believed, accelerations of the FHR and good baseline variation are present from as early as 20 weeks.

Fetal tachycardia

In this project, basal heart rate from all analysed recordings ranged between 132-171 bpm. Due to the undetermined clinical relevance of a fetal tachycardia at these early gestations, we did not exclude a basal or mean heart rate more than 160 from our data for final analysis.

We noticed a total of 8 recordings (2.8%) with fetal tachycardia (according to term criteria) in our initial data collection pool, of which 6 were borderline (all 6 recordings had a basal heart rate of 161 bpm) and two were significantly higher (164 bpm and 171 bpm).

Although all 8 of these recordings resulted in live-born babies, it was noticed that 3 of these fetal tachycardic recordings resulted in preterm deliveries, so they were subsequently removed from the data submitted for final analysis on the basis of adverse pregnancy outcomes:

Table 5: Recordings depicting a fetal tachycardia

<u>Gestation at recording (days):</u>	<u>Basal fetal heart rate (bpm):</u>	<u>Birth weight (gram):</u>	<u>Gestation at birth (days):</u>	<u>Gestation at birth (weeks):</u>
164	171	2700	280	40w0d
156	161	2800	274	39w1d
163	161	3500	270	38w4d
161	161	2900	271	38w5d
161	161	2000	242	34w4d
148	161	1506	227	32w3d
166	164	2530	249	35w4d
165	161	2820	270	38w4d

Of these 3 preterm deliveries, 2 were delivered by emergency caesarean section and one with assisted forceps delivery. Unfortunately we did not have information regarding the indications for early delivery. However, none of these reflected growth-restriction according to population specific growth percentiles for birth weight. ⁽¹⁵⁾ All 5 of the other “tachycardic recordings” resulted in uncomplicated normal vaginal deliveries at term and were therefore included in the data-pool for final analysis.

Accelerations and decelerations

Although the presence of accelerations in fetal heart rate tracings at 20 weeks gestation has been documented before, the authors often concluded that the occurrence of decelerations are more frequent than accelerations in these early fetal heart rate recordings. ^(4, 7, 11, 18)

With the program-specific software, we applied the Dawes-Redman criteria (which has been reviewed and established as an accurate tool in computer analysis of Cardiotocographic recordings through the Oxford analytical system since 2002 ⁽⁵⁾), defining a positive deviation from fetal baseline of at least 10 bpm for a minimum of 15 seconds as a “small acceleration” and a positive deviation from fetal baseline of more than 15 bpm for at least 15 seconds as a “large acceleration” in our analysis.

Table 6: Pre-programmed definitions of accelerations and decelerations

	<u>Amplitude (beats per minute):</u>	<u>Minimum time (seconds):</u>
Small acceleration	➤ 10 bpm	➤ 15 seconds
Large acceleration	➤ 15 bpm	➤ 15 seconds
Small deceleration	➤ 10 bpm	➤ 60 seconds
Large deceleration	➤ 20 bpm	➤ 30 seconds

Due to the individual length of each recording varying between 30 and 96 minutes (as previously discussed), in order to standardise the occurrence of accelerations and decelerations each recording was assessed for the total number of accelerations or decelerations (small and large) as well as the average amount per 10 minute intervals.

Decelerations were also categorised as small (negative deviation from fetal baseline of at least 10 bpm for a minimum of 60 seconds) and large (negative deviation from fetal baseline of at least 20 bpm for a minimum of 30 seconds) with 67% of the total analysed fetal heart rate recordings showing the presence of decelerations and seemingly no clinical implication considering all these pregnancies had good neonatal outcome.

Figure 9: Small decelerations (total recording)

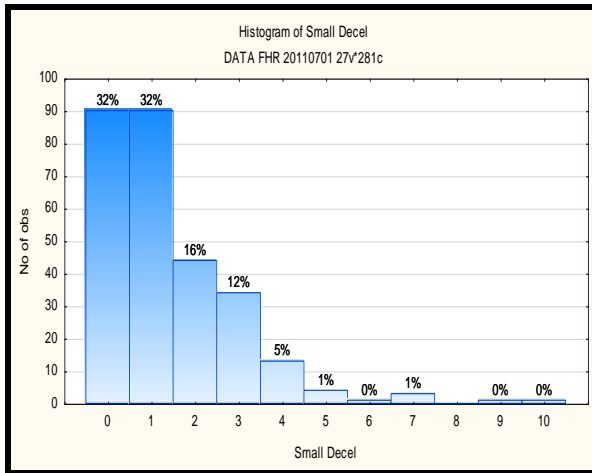


Figure 10: Small deceleration (standardised per 10 min)

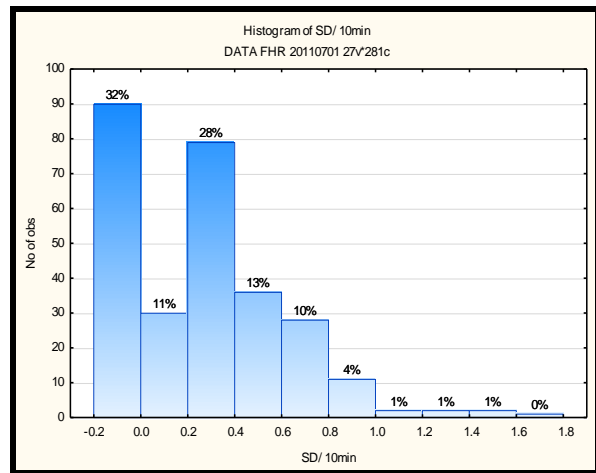


Figure 11: Large decelerations (total recording)

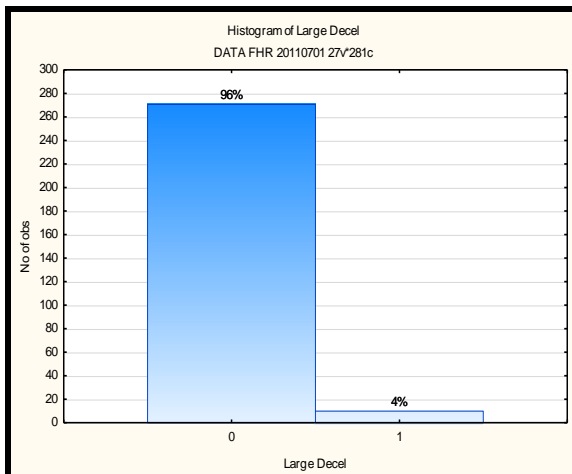
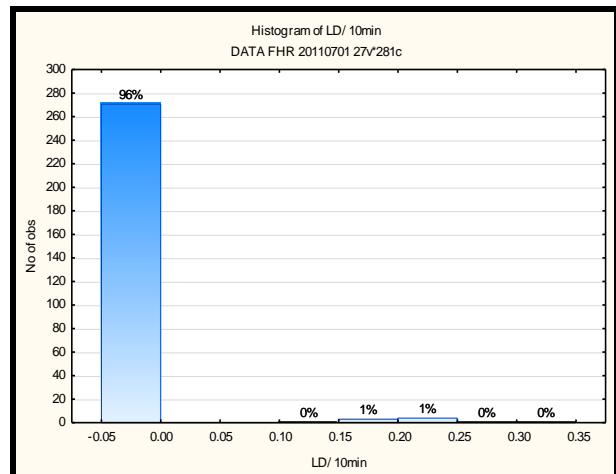
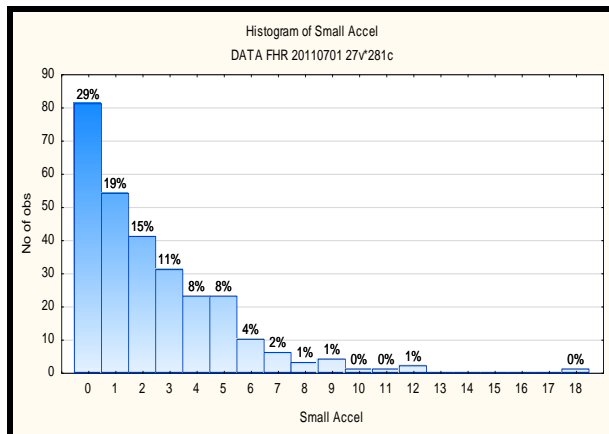


Figure 12: Large decelerations (standardised per 10 min)

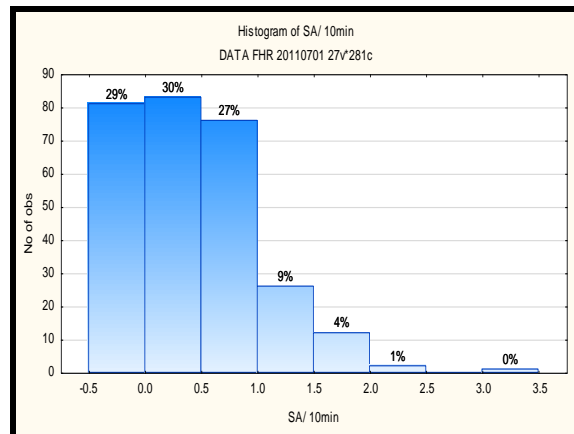


We found accelerations between 20-24 weeks gestation to be a noticeable occurrence with 71% of recordings showing accelerations in these very early gestations. The frequency of small accelerations standardised per 10 minutes of recording were 0.5 and large accelerations 0.1.

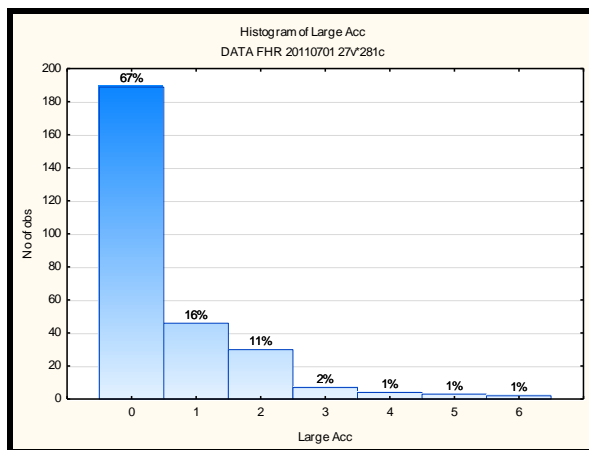
**Figure 13: Small accelerations
(per total recording)**



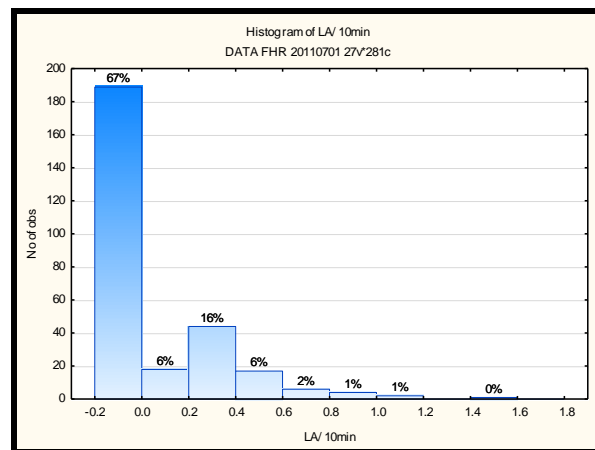
**Figure 14: Small accelerations
(standardised per 10 min)**



**Figure 15: Large accelerations
(per total recording)**



**Figure 16: Large accelerations
(standardised per 10 min)**



This showed the presence of accelerations to be more frequent than decelerations with the frequency of small decelerations 0.3 per 10 minutes and large decelerations 0.008 per 10 minute intervals.

These findings are in contrast with early publications. Although some earlier publications used different definitions concerning amplitude and duration, which makes a direct comparison with our data difficult, the DK 1.4a pre-programmed DR parameters we used are the accepted definitions for electronic fetal heart rate evaluation and interpretation in current literature and correlates with parameters set by Pardey for numerical analysis of FHR patterns. ⁽⁵⁾

Variability

It is well accepted in literature, as well as in clinical management, that cycling between active and quiet sleep (a primary indication of fetal well-being) as measured by the presence of high fetal heart rate variation, accelerations and clusters of fetal movements, is present and quantifiable from 28 weeks gestation. Beat-to-beat variation is the irregularity of the FHR caused by the normal variance in intervals between consecutive cardiac cycles as triggered by a sympathetic and parasympathetic push-pull effect. Measurement from the fECG is the gold standard for short-term variation (STV).⁽⁵⁾ The presence of good short term variation (STV) is a reassuring feature irrespective of how short the recording is, as it is a sign of intact neurologic modulation of the FHR and of normal cardiac responsiveness. Also, a definite correlation exists between poor STV and metabolic acidosis at birth or intrauterine death.⁽¹⁹⁻²¹⁾

Figure 17: Short term variation (milliseconds)

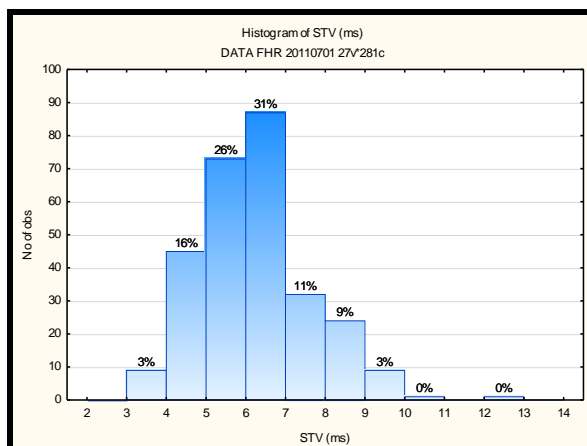
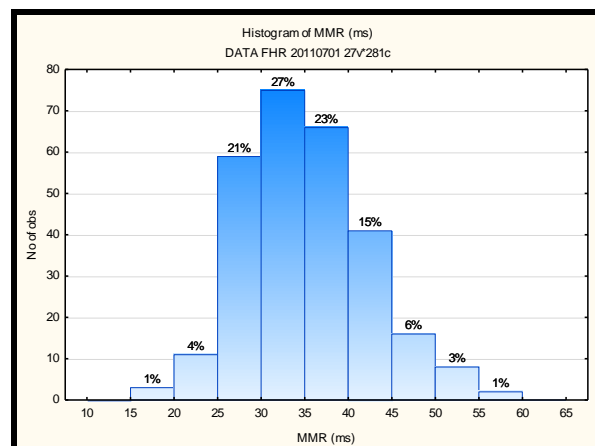


Figure 18: Mean minute range (milliseconds)



We found a mean STV of 6.2 msec (SD 1.4 msec) and range from 3.2 to 12.7 msec. Normally the STV should be > 3.0 msec. If it is < 4.5 msec, the long-term variation should be above the 3rd percentile for that gestational age. ⁽⁵⁾ It is therefore clear that abnormal values are not generally seen in spite of very early gestational ages. Poor variation before 24 weeks should therefore be regarded as outside the normal range and not caused by immaturity as such.

The minute range is the maximum difference between highest and lowest point of FHR/minute and the average of consecutive minute ranges is the mean minute range (MMR) which is used as a measure of long-term variation (LTV). We found a median value of 34.6 msec with a range between 17.5 msec and 58.2 msec. Although some cases were below the recommended 32 msec, it should be remembered that the 32 msec was derived from information obtained later in pregnancy. ⁽⁵⁾

The wide range of values, as we found in STV, could be explained in different ways. Firstly, it could be explained by different states in which the fetus was during the recording as rest-activity cycles have been documented from as early as 24 weeks and active states and REM sleep are associated with a higher variation in contrast to quiet sleep. ^(17, 18)

Secondly, the wide range in LTV could be explained by differences in gestational age when the recordings were done. Unfortunately we could not investigate this effect as the gestational ages were clumped together around 23 weeks with few cases around 20 weeks. The reason for this is that bookings for the 20-23 6/7 weeks study visits were made as late as possible in this time window as it is easier to assess fetal facial dysmorphology by 3-D ultrasound, an essential assessment in the Safe Passage Study, as late as possible in the time window.

Thirdly, there could have been individual variation, although the gestational ages and states could have been the same, indicating different starting points of central nervous system maturation of the fetus. It is unlikely that the fetuses with low LTV were severely compromised as no STV below 3.0 msec was found and they were all born alive at 37 weeks or later and also as fetuses with low birth weights or who were small for gestational age have been excluded. In this study the LTV between term and preterm deliveries could not be compared as preterm deliveries were excluded from the analysis. However, we plan to investigate this when study numbers are greater.

Low FHR variation is usually observed during periods of quiet sleep of the fetus. ⁽²²⁾ According to the Dawes Redman analyses, a period of low variation is identified when the

mean minute range in at least 5 of 6 consecutive 1-minute intervals is less than or equal to 30 milliseconds. A period of high variation is identified when the mean minute range in at least 5 of 6 consecutive 1-minute intervals is more than or equal to 32 milli-seconds. ⁽¹⁸⁾

The median proportion of a state of high FHR variation was 16.7%, ranging from 0% to 94.9%. A state of low variation was seen during 21.4% of the recordings, ranging from 0% to 100% of the recording time. De Vries at al. studied diurnal and other variations in fetal movement and heart rate patterns at 20-22 weeks. ⁽¹¹⁾ Significant diurnal changes were observed with the lowest values in the morning and the highest values during the evening. As we did all our recordings during the morning and early afternoon, our findings were done when the fetus was less active. In general, the limited number of previous studies on FHR patterns before 26 weeks gestation found reduced FHR variation and diminished acceleratory response to stimuli. ^(4, 11-14)

Preterm labour

Preterm delivery is defined as delivery before 37 completed weeks or 259 days gestation. According to the 2008-2009 Saving Babies report, preterm birth contributes to 21% of South African perinatal mortalities and still is a major public health issue. A literature review confirmed the incidence of preterm labour (PTL) in Africa to be estimated at 11.9 % and for this specific study population in Bishop Lavis we found 10.5% of all deliveries occurring before 37 completed weeks. ⁽²³⁻²⁵⁾

The incidence of preterm delivery in this study population was found to be 13.4% (a total of 55 participants excluded before final data analysis). As the occurrence of preterm deliveries was only identified as an adverse pregnancy outcome for the purpose of this project, further investigation into epidemiological factors as well as analysis of these specific fetal heart rate patterns were not done.

On-going study into the seemingly high incidence of PTL in this population is warranted. Investigations into social as well as racial factors contributing to early delivery could contribute greatly to improved healthcare provision for this population.

Low birth weight

In this study, low birth weight babies specifically referred to term deliveries (deliveries after 259 days) that were below 2500g. Twenty-two participants were excluded from final analysis due to low birth weight at term according to the WHO standardised 2500g cut off (5.3% of initial 411 recordings). (See Table 1)

The population estimates for low birth weight infants in sub-Saharan Africa is currently estimated at 15 %.⁽²⁶⁾ However, no distinction is made in current literature between low birth weight deliveries due to preterm births vs exclusively term low birth weight infants. When calculating our total incidence of low birth weight (delivery weight less than 2500g) we had an incidence of 13.6% (a total of 56 recordings) which is below the estimate for this region as referenced above.

However, the normal distribution for birth weights also vary according to geographical groups or population and in order to be sure we focussed our analysis on uncomplicated pregnancies as far as possible, we cross-referenced all delivery data with population specific growth curves as described by Theron *et al.* for the area served by Tygerberg obstetrical services.^(15,27) A total of 39 participants were excluded from analysed data due to population-specific low birth weight (9.5% of initial 411).

We did not analyse maternal weight and height in association with birth weight which according to Mikolajczyk *et al.* should also be a consideration when evaluating fetal outcomes through weight at delivery.⁽²⁷⁾

Fetal demise

A total of 11 unexplained intra-uterine fetal deaths (IUFD) occurred in this study population of 411 and were excluded before final data analysis (2.7%) which falls below the documented global statistics. Although global estimates of the incidence of stillbirths are constantly underestimated due to lack of data capturing (with only about 2 % of IUFD globally counted through vital registration) the stillbirth incidence for sub-Saharan Africa is documented as 3.4%.⁽²⁴⁾

An additional 2 recordings were excluded due to neonatal demise (0.5%). The first of these were born at term (birth weight 2880g) with Apgar scores of 8 and 9 at 1 and 5 minutes respectively. The baby demised at 2 months and 3 weeks, but unfortunately we did not have any further information regarding the circumstances surrounding the demise.

The second of these two neonatal deaths was a preterm delivery at 229 days (32 weeks 5 days) with a birth weight of 1300g which died at day 10 of life in a tertiary care facility of which we unfortunately also did not have any further information regarding final cause of death.

As the focus of the Safe Passage Study is the evaluation of maternal high risk behaviour on adverse pregnancy outcomes (specifically IUFD and Sudden Infant Death syndrome (SIDS)), new insight into preventable causes of these adverse outcomes might be available soon.

Conclusion

With the Monica AN24 Transabdominal Fetal Monitor and product specific software we successfully assessed and analysed the FHR patterns according to the Dawes-Redman criteria employed at later gestational ages. Clear patterns of FHR change and quantifiable parameters of heart rate variability were consistently observed.

In contrast to what has previously been documented, accelerations of the FHR and good baseline variability are present from as early as 20 weeks.

The isolated presence of decelerations in numerous recordings did not necessarily predict a detrimental outcome.

Information from this study provides an important foundation for further studies of early FHR patterns and it will help us better assess the fetus at a crucial age for indicators of good perinatal outcome.

Recommendations

Considering the growing number of recordings available through the ongoing Safe Passage Study, we would like to do a follow up study of similar design using the most recent product specific software (Currently DK 1.8 vs 1.4a that was used in this project) to validate our findings through larger participant numbers.

This might make the analysis and comparison of FHR patterns in weekly intervals possible which will enable us to further investigate the maturation of the autonomic nervous system in these pre-viable fetuses and the detectable effect thereof on cardiac function.

The following additional studies will be possible once these parameters have been validated against good perinatal outcome and uncomplicated term pregnancies and as soon as data from the PASS network will be made available for publication:

1. Evaluation of FHR patterns in early pregnancies resulting in preterm labour. Looking into possible predictive parameters for early delivery.
2. Effect of maternal high risk behaviour/in-utero exposure to smoking and alcohol on FHR patterns at early gestations.
3. Predictive value of FHR deviations (in comparison to normative values, as established by this study) to adverse neonatal outcomes (unexplained stillbirths and early neonatal deaths).

Abbreviations

BPM - beats per minute

CTG - Cardiotocography

ECG - Electrocardiography

FHR - Fetal heart rate

fECG - fetal Electrocardiography

IUFD - Intra-uterine fetal death/demise

MSB - Macerated stillborn baby

NICHD- National Institute of Child health and Human Development

PTL - Preterm labour

SIDS - Sudden Infant Death Syndrome

STV - Short term variability

TBH - Tygerberg Hospital

IUFD - Intra uterine fetal death/demise

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