UNIVERSITÀ POLITECNICA DELLE MARCHE

INFORMATION ENGINEERING DEPARTMENT

MASTER DEGREE IN BIOMEDICAL ENGINEERING

TOWARDS PHASE-RECTIFIED SIGNAL AVERAGING TECHNIQUE FOR FETAL HEART-RATE SIGNAL PROCESSING

Supervisor

Dr. Laura Burattini

Co-supervisors

Dr. Agnese Sbrollini

Dr. Massimo Walter Rivolta

Student

Elisa Brizzola

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Abstract

Pregnancy is a truly delicate condition, both for the woman and for the foetus, which are subjected to a series of risks from the embryogenesis and the foetus formation, up to the childbirth. Each of these stages needs a precise set of tests, analysis and monitoring procedures, to limit the risks and check that the physiological parameters are maintained.

In this present study, the focus is on the labour, so what nearly precedes the delivery itself, since this phase could be crucial for the positive outcome of the birth. Problems that could present in this time, as a reduced oxygenation of the foetus, could, in fact, bring to pathological states as hypoxia or acidosis, which could be extremely negative events for the child wellbeing.

Monitoring the foetus's fetal heart rate, together with the uterine contractions recording during labour, using a cardiotocograph, is a valid solution to keep the FHR parameters of the foetus under control and to determine the occurrence of eventual worrying features of the tracks. However, this procedure is still based on the personal interpretation of the medical personnel, which follows the FIGO guidelines for CTG feature identification, such as the presence of accelerations and decelerations, but keeps a certain level of subjective evaluation, based, for example, on the different experience or formation of the doctor.

To overcome this subjectivity, the aim of the research is to find an automatic method to correlate the occurrence of specific CTG features to certain risk factors, to allow clinicians to identify and predict critical conditions, in which it is necessary to intervene with a Cesarean cut.

This study, in a particular way, wants to determine the values of the deceleration reserve (DR), which is an index calculated from the sum of acceleration (AC) and deceleration capacities (DC). These two parameters are derived by the application of a methodology called Phase Rectified Signal Averaging (PRSA), which allows to extract and average intervals of signal, in our case foetal RR series, obtained from the CTG recordings of the FHR.

Once DR is derived for each subject, it is correlated to the three neonatal post-partum parameters, pH, Base Excess and Apgar score, which provide information about the health state of the child as soon after the birth accomplishment. R and *p-values* are obtained for each couple DR/pH, DR/BE, and DR/Apgar, showing, respectively, values of 0.05 for the correlation DR/pH, -0.04 for DR/BE, and 0.14 for the R-value and of 0.09 for DR/pH, 0.14 for DR/BE, and $< 10^{-5}$ for DR/Apgar for the *p-value*.

These results express a lack of significant and reliable correlations between DR and any of the three neonatal post-partum parameters, meaning that the aim of the study seems not to be accomplished, using this specific approach.

Further evaluations could be done, for example considering a different index instead of DR, as well as the possibility to use different parameters to correlate. The possibility to correlate FHR features, analysed through CTG recordings, to neonatal post-partum parameters is therefore not completely excluded but left to further and different approaches.

A future perspective could be, for example, the possibility of considering introducing in the method the recording of uterine contractions, which were not evaluated in this study.

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Introduction

During pregnancy, from the first stages until labour, the foetus, as well as the mother, are subjected to a series of risks, that could compromise the childbirth outcome. For these reasons, the medical personnel should warn from the very first the family of everything that is necessary to take care of, in order to avoid, or at least limit, any of these risks. Periodical exams are recommended, depending on the different characteristics of the pregnancy, like the woman's age, the presence of other pathologies or complications.

Among these monitoring techniques, cardiotocography (CTG) has shown its advantageous properties and has gained acceptance among the scientific community. Used especially during labour, CTG allows to record fetal heart rate and uterine contraction simultaneously, to have an overview of the condition of the foetus from the variation of his heartbeat, also depending on the contractile activity of the womb, to facilitate the childbirth accomplishment. As a matter of fact, it is relevant to control the conditions of the foetus, to have the possibility to intervene in case some unexpected events occur, for example deciding to perform a Cesarean cut.

These decisions are still taken from the majority based on the personnel's experience and, even if there are international protocols and guidelines, most of the interventions depend on the doctor's decision.

For example, it is known that accelerations and decelerations of the FHR can be red flags for improper oxygenation of the foetus, which can result in hypoxia and acidosis. Although the community of gynaecologists and obstetricians follow some common regulations, as the FIGO guidelines, identification of parameters as acceleration or deceleration onset and offset, as well as the evaluation of the severity of the risk, are often left to the personnel judgment and not always completely objective and unquestionable. This could bring to different protocols during critical labours, sometimes performing Cesarean cuts in cases in which it could be avoided and increasing the risks factors without a concrete advantage.

In order to solve interpretation issues, the research has been concerned on studying the CTG tracks and features, with the aim to find a way to make the identification process the more objective and automatic as possible. A solution of this kind would in fact help the clinicians' job, by providing an automatic recognition of features, as the previously mentioned accelerations or decelerations, limiting the human error, for instance due to the difference of experience, of interpretation, of what could banally be a mistake made by the doctors for the stress of a critical situation as the labour could often be.

A further step is the introduction in the research of other parameters, which are not taken from

the CTG recording, but are important to evaluate the child wellbeing. Most of them are acquired from blood samples, so they can be obtained only after the breaking of the membranes and the beginning of labour or after the birth, as it is for pH or Base Excess, or acquired observing a set of characteristics of the baby as soon after the birth, as for the Apgar score.

Identifying a correlation between the positive or negative birth outcome and CTG parameters could be a significant breakthrough for an automatic analysis of the continuous recording acquired during labour, allowing to act and do Cesarean cut or similar procedures just when it is really necessary and avoiding useless emergency trials, that could only increase the hazards in an already critical situation.

In this particular study, the goal is to extract RR intervals, converting FHR form the CTG recordings, to derive Deceleration Reserve. DR is an index given from the sum of deceleration and acceleration capacities (DC and AC), that are two parameters derived from the application of Phase Rectified Signal Averaging on RR intervals.

Obtaining DR any time accelerations, decelerations, or both, are identified on the CTG recordings could be a useful tool for a possible practical application, in order to use it in monitoring during labour, as a warning of critical states of the foetus itself. That is why it could be helpful to identify a possible correlation between the DR and the neonatal post-partum parameters, as pH, BE and Apgar, to predict the occurrence of hypoxia or acidosis before the complete accomplishment of the delivery.

While the fact that pH, BE and Apgar can be quantified just once the infant is born, so when eventual damages to his wellbeing could have already occurred, identifying a correlation between them and recording parameters that can be read before the childbirth, could mean a significant danger decreasing.

The aim is to find a way to reduce unfortunate outcome to the bare minimum, thanks to a proper and precise monitoring that would be able to permit to the doctors to perform just those procedures that are necessary and as useful as possible for each specific woman and her new-born.

Chapter 1

Pregnancy, foetal development and childbirth

Pregnancy

Anatomy of the female reproductive system

The role of the female reproductive system *(Abrahams et al., 2010)* is double: the ovaries produce germ cells (oocytes) for fertilization and the uterus nourishes and protects each resulting foetus for the 9 months of the gestation. The apparatus consists of the internal and external genitalia. The latter part, also called vulva, is the site where the reproductive tract opens to the outside. The vaginal opening is located posterior to the opening of the urethra, in an area known as the vaginal vestibule, lined with two folds of skin on each side, the labia minora and labia majora, in the front of which the clitoris is located. For what regards the internal genitalia, they are located inside the pelvic cavity and protected by the bony ring that forms the pelvis. They are composed by the ovaries, sites of the production of oocytes and located on each side of the uterus; the fallopian tubes, which receive the oocytes and carry them in the uterus; the vagina, which connects the cervix to the vulva and can dilate a lot, as in the childbirth, and the uterus.

The uterus is made up of two parts: the body, which forms the upper uterus, it is quite mobile as it expands during pregnancy and accommodates the openings of the fallopian tubes; the cervix, the lower part of the uterus, which is a thick muscle canal anchored to the surrounding pelvic structures. The wall of the body of the uterus has three layers: the perimetrium, a thin outer covering that represents the continuation of the pelvic peritoneum; the myometrium, which forms the mass of the uterine wall; the endometrium, the inner lining that allows the implantation of an embryo in the event of a successful fertilization. In case of pregnancy, the uterus dilates by pushing the abdominal organs to the side against the diaphragm and the thoracic cavity towards the top. Organs such as the stomach and bladder are compressed to a limit such that their capacities are decreased. For the first 12 weeks the dilated uterus remains inside the pelvis, in 20 weeks it reaches the umbilical region and towards the end of pregnancy it can reach the xiphoid process, the lowest part of the breastbone.

Its weight increases from 45g to 900g, the myometrium grows as the fibers increase in number

and size. At the end of pregnancy, the uterus recovers its initial dimensions of about 7.5 cm in length and 5 cm in width.

Fertilization

The beginning of pregnancy *(Pescetto et al., 1989)* sees its first phase in the migration of spermatozoa, released at the end of the process of spermatogenesis in the seminiferous tubules of the male genital system. They migrate in the cones or efferent ducts, to then be pushed and deposited in the epididymis. To be able to penetrate into the oocyte and fertilize it, the spermatozoon must undergo a series of transformations in the female genital tract and precisely the capacitation and the acrosome reaction, which will allow it to merge with the oocyte. Then the sperm reaches the pellucid zone of the oocyte, consisting of a looser outer layer and an inner one in direct contact with the perivitelline space, which separates the zona pellucida from the plasma membrane of the oocyte. The zona pellucida has receptors specific for spermatozoa, which adhere and penetrate in this region. At this point the sperm is in the perivitelline space, where the cytoplasmic membranes of the two gametes merge. Thus, they form the female and male pronuclei, which approach following a network of microtubules converging to the spindle. DNA replication occurs, preparing to the first division of segmentation. The disappearance of the membrane of the two pronuclei occurs during this prophase division, approximately 24 hours after fertilization. The pronucleated oocyte becomes the zygote, the first cell of the embryo with 46 chromosomes. The zygote remains 2-3 days in the tubal ampulla and goes toward the first mitotic divisions. Subsequently the embryo is transported through the isthmic region and reaches the uterus, where it will implant.

The embryo

The pre-embryo *(Pescetto et al., 1989)* is defined as the product of the union of the two gametes from the moment of the fertilization to the appearance of the embryonic axis. After the 14th day until the end of the 8th week of development[1] we talk about "*embryo*" and after it starts to be defined as "*foetus*". The development begins with the presomitic state, which goes until the 20th day of conception age. At this stage, the embryonic disc and the amniotic cavity are formed. From the 20th to the 30th day, the development of the human embryo is characterized by the formation of somites, which progressively increase in number until generally reaching 44 units.

[1] The term "development" is commonly used as a synonym for conceptional age, which is the duration of pregnancy calculated from the day of ovulation. By gestational age, on the other hand, we mean the duration of pregnancy calculated from the last menstruation. Therefore, the conceptional age is on average 14 days lower than the gestational age.

From them, most of the skeleton and striated musculature will be formed. During the 3rd week of development, the embryo begins to have a more defined shape and appears as a more or less regularly cylindrical body, interposed between the amniotic cavity and the cavity of the yolk sac. Around the 4th week, the sketch of the heart, that of the eye, the forebrain, the liver, the kidney and of the outer ear begin to be evident. At the end of the 5th week the sketches of the upper and lower limbs are well evident, and the umbilical cord is perfectly formed. Between the 6th and the 7th week of gestational age, the heart already presents rhythmic pulsations; however, there is reason to believe that the former heart contractions occur during the 4th or 5th week. At the end of the 8th week of development, the embryonic body shows the sketches of the bones, muscles, nerves and great vessels. The cephalic extremity begins to separate from the thorax and nose, ears and jaw can be distinguished

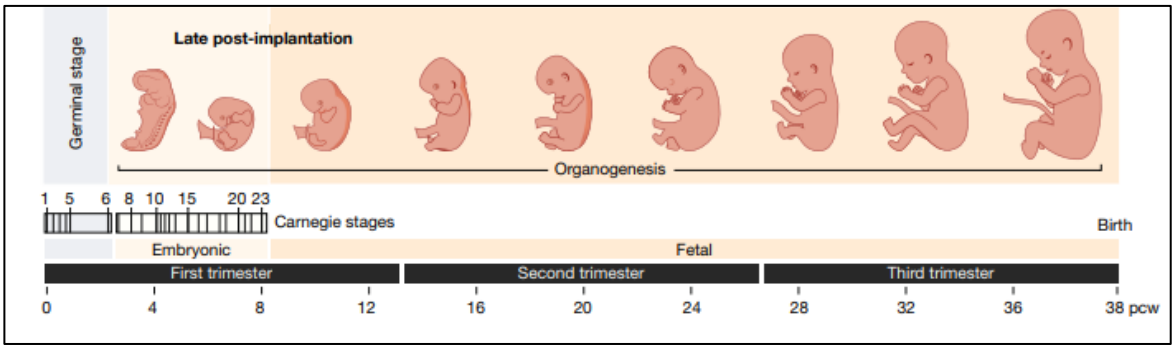

Figure 1. Human embryo development (Adapted from Haniffa et al., 2021)

Development of the foetus

The stages of growth of the foetus

At the end of the 12th week of gestational age *(Pescetto et al., 1989),* the eye sketches are covered by the eyelids; the extremities are articulated in their various segments and begin to present the first active movements. Complete differentiation of the internal genitalia has occurred. The whole body of the foetus takes on human appearance. At the end of the 16th week, the intestinal canal has a greenish content, meconium. There is the definitive differentiation of the external genitalia; The skin is thin and transparent, completely hairless. At the end of the 20th week, the active fetal movements are so lively that they are perceived with abdominal palpation. Even the fetal heartbeat can sometimes be heard, by means of the obstetric stethoscope. The cephalic extremity is still bigger, in relation to the rest of the body, even if the degree of disproportion

is less pronounced than in the previous weeks. The 20th week is considered to be the lower limit for a foetus to be able to survive, in some, even if rare, cases, after separation from the maternal organism. At the end of the 24th week the skin is wrinkled, but the first fat deposits begin to form. During the weeks from the 25th to the 28th, the foetus reaches a degree of maturity that in a percentage of cases (about 10-30%) can allow survival in the event of preterm childbirth. At full 28 weeks, if fetal weight is appropriate, i.e., on the order of 1000 g, the chances of survival can reach 60%. At the end of the 32nd week, the skin is less wrinkled, but it is still covered with fluff. The chance of survival in the event of preterm birth is between 50% and 90% up to the 34th week, significantly improving during the 35th week. At the end of the 36th week, the body takes on rounded contours for the deposition of subcutaneous adipose tissue and the skin loses its wrinkled appearance.

At the end of the 40th week the normal foetus has reached maturity. It will therefore have the following characteristics: the body length varies between 48 and 52 cm, weight varies between 2800 and 4000 g, maximum skull circumference is on average 34.5 cm, the circumference of the shoulders is about 35 cm, the pelvic circumference of 29-30 cm, the colour of the skin is white-pink; in the mature foetus there are also some functional activities such as the ability to breathe and use the gastrointestinal apparatus normally.

The cardiovascular development of the foetus

The fetal circulation *(Pescetto et al., 1989)* in the second half of pregnancy has some divergent peculiarities from the adult circulation. The umbilical vein carries arterial blood from the placenta to the foetus, this blood became arterial crossing the chorionic villi, where it took oxygen from the maternal blood and eliminated carbon dioxide. The blood from the umbilical vein, penetrated through the navel into the fetal body, flows partly to the liver by means of the branch communicating with the portal vein and partly, through the venous duct of Aranzio, it flows directly into the ascending vena cava. The two flows join above the liver because the blood that has passed through the liver also reaches the vena cava via the hepatic veins.

From the ascending vena cava, blood enters the right atrium, which has a formation called the Eustachian valve. Through it the blood coming from the ascending vena cava is sent towards the interatrial septum; in fact, in the heart of the foetus, there is the Botallo forum, which connects the two atria. Then the blood comes into the left ventricle and from there into the aorta, from which it goes on the right into the brachiocephalic trunk and on the left into the carotid and subclavian, to distribute in the upper part of the fetal body. The other part of blood is instead

conveyed through the descending aorta in the lower 2/3 of the body.

Blood discharged from the upper fetal body returns to the right atrium through the descending vena cava, then goes into the right ventricle and through the pulmonary artery a small amount of blood reaches the lungs, which are cooperative and functionless in the foetus. Instead, most of the blood flow is diverted into the aorta by the presence of a duct, the Botallo arterial duct. Some of the blood will eventually be channelled into the umbilical arteries and will be distributed in the chorionic villi to undergo the oxygenation process.

After giving birth, radical transformations of the cardio-circulatory system of the foetus are established, due to the beginning of respiratory activity, such as the obliteration of the Botallo arterial duct, which established a communication between the pulmonary artery and the aorta, the closure of the duct of Aranzio, which established a communication between the umbilical vein and the ascending vena cava and the closure of the foramen of Botallo, which established interatrial communication.

Regarding the heart, already after the 7th week the cardiac activity can be recorded with the use of ultrasound equipment. Between the 7th to and the 8th week the frequency is of the order of 130-150 beats per minute (bpm), between the 9th and the 11th week, it reaches values of 160-175 beats per minute, then it drops again to values of 145-155 bpm between the 12th and 14th week. In the second half of the gestation, the fetal rate remains fairly constant, between 120 and 160 bpm. The blood flow in the umbilical vein is of the order of 120 ml / kg / min between the 26th and 35th week, then gradually decreases and at the end it is about 90 ml / kg / min .

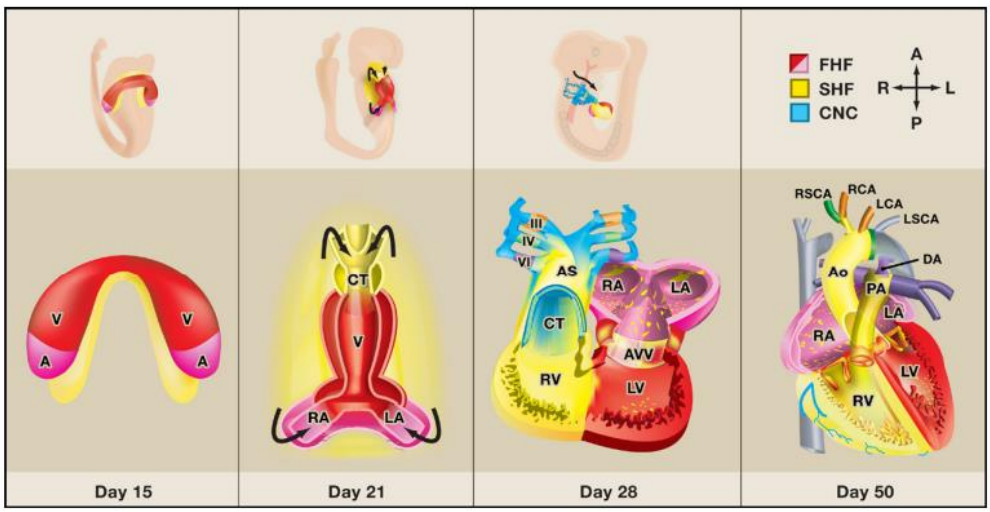

Figure 2. Human cardiac development (Srivastava, 2006)

Nervous development of the foetus

The nervous system *(Bolender & Kaplan, 2017)* starts forming about 18 days after fertilization, making it the first system to start its development. First, there is a thickening of the ectodermal path along the caudal cranial axis of the embryo, in the area destined to become the cervical region. This thickening is the result of an increase in the height of the cells of the ectoderm as they change shape from cuboidal to columnar. An oval area of thickened ectoderm, called neural plaque, is obtained. Two crests of this neural plate on each side of the midline, start to grow, giving rise to two longitudinal neural folds with a central neural sulcus. These neural folds increase in height, curving towards each other, touching and merging to form the rudiment of the neural tube halfway along the embryonic axis. The remaining unused ends of the neural folds are called cranial and caudal neuropores because the neural tube is open in correspondence of these sites. The cranial neuropore closes on day 25 and the caudal neuropore on day 27 of development.

Soon after the fusion of the neural folds in a given region of the embryo, the neural tube separates from the ectoderm and the mesenchyme is hidden below the surface. The actual neural tube continues to form the central nervous system, which consists of the brain and spinal cord, while the neural crest forms a large part of the peripheral nervous system, consisting of portions of autonomic, cranial and spinal ganglia, and nerves.

The lumen of the neural tube becomes the central canal of the spinal medulla and of the ventricles of the brain. The spinal cord develops from the neural tube, which assumes a C-shape in lateral view after about 30 days. The tube wall thickens and soon stratifies in a ventricular zone, that borders the central canal, an intermediate zone and a marginal zone. The intermediate zone is created by the migration of neurons from the ventricular zone. These neurons send out processes that create the marginal zone, which later becomes the white matter of the spinal cord. The spinal cord extends along the entire length of the development of the vertebral spine, during the embryonic period. However, the spinal cord grows slower than the spinal column and thus, in the fetal period and beyond, these two structures change their position. After 24 weeks, the spinal cord extends caudally to the level of the first sacral body. In the new-born, it extends to the third lumbar vertebral body, in the adult it extends up to the first lumbar vertebra.

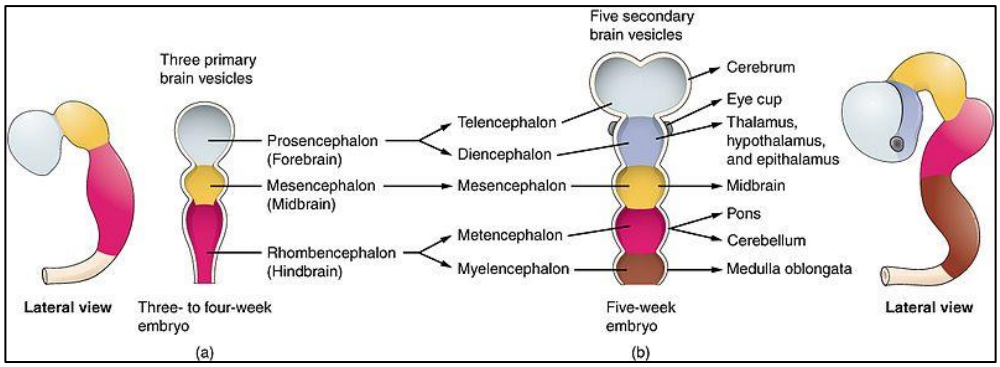

Figure 3. The five secondary brain vesicles and their derivatives (Barnes, 2018)

The brain is divided into the anterior brain (forebrain), middle cerebrum (midbrain) and hindbrain, when flexion of the midbrain appears. These three divisions of the brain quickly become five, namely telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon. Two distinct centers of origin of the signals organize the cranial portion of the neural tube. One controls the front brain, the second one the hind brain.

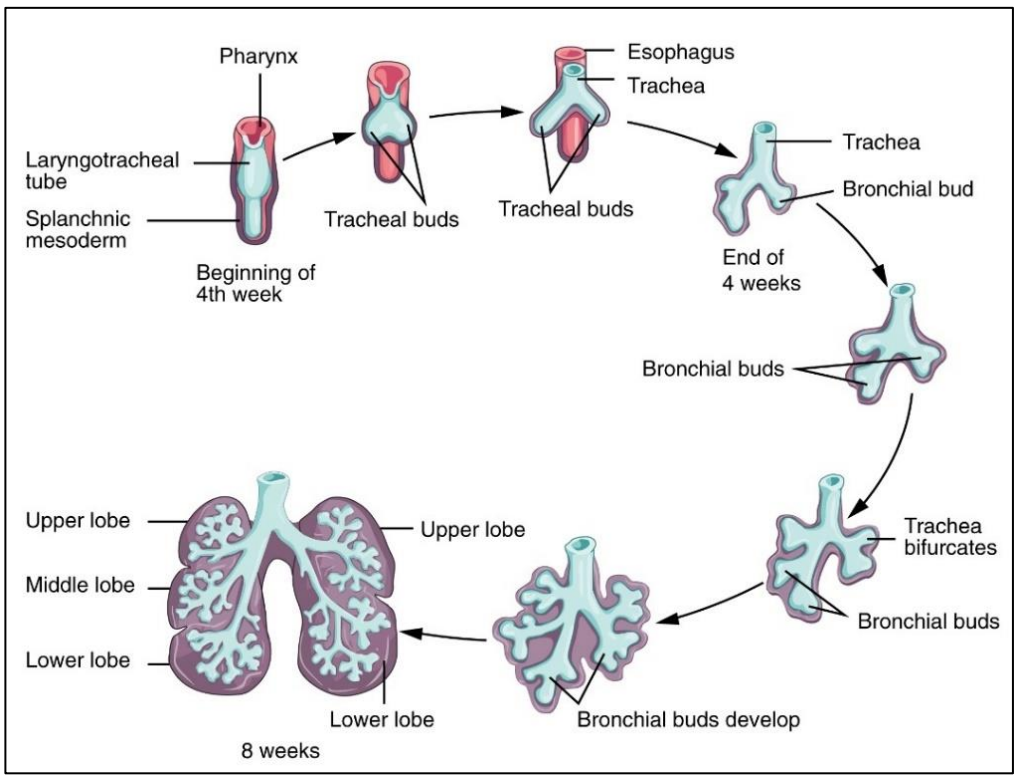

Figure 4. Development of the respiratory system (Biga et al., 2019)

The respiratory development of the foetus

The lung *(Pescetto et al., 1989)* does not perform any function during fetal life. However, it

undergoes a progressive maturation, which allows it to face the beginning of autonomous breathing even if delivery takes place long before the end of gestation. The validity and the possibility of duration of the postnatal lung function, however, are lower, as lower is the gestational age. In addition to the morphological evolution of the lung structure, the development of surfactants substances has decisive importance produced by the walls of the alveoli, which give the lung parenchyma the properties that are physical indispensable to perform its task efficiently. Such surfactants consist of a complex of phospholipids, traces of which can be already found around the 20th week of gestation; however, they reach a functionally adequate level only after the 30th week of gestation.

Childbirth

Labour and uterine contractions

During the last weeks of gestation, a certain uterine contractile activity takes place *(Pescetto et al., 1989)*, with characteristics that gradually acquire the coordination and rhythmic notes of the labour. Pre-labour is therefore a period that cannot be determined both as a beginning and as a passage to the prodromal period of actual labour. An acceptable criterion is that of assuming as the starting point of the prodromal period the moment when the contractions become rhythmic, coordinated and perceived with an annoying sensation, bordering on pain, by the pregnant woman. Such phase lasts on average about 8 hours in nulliparous women (women who have never given birth) and about 5 hours in pluriparous (women who have given birth several times), but it is not always possible to make an exact calculation for the practical difficulty of objectively defining the starting time.

The dilation period corresponds to the active phase of cervix dilatation and in it we can distinguish three secondary phases of acceleration, maximum activity and deceleration. Uterine contractions become increasingly frequent and prolonged and the painful sensation increases. The average length of the dilation period in nulliparous is 4-5 hours, in multiparous it is about two hours.

Expulsive and post-partum phase

When the uterine mouth is fully dilated, the expulsive period *(Pescetto et al., 1989),* which is characterized by the development of the main mechanical phenomena of childbirth, begins. The uterine contractions are also normally associated with voluntary pushes by the muscles of the abdominal press. The duration of the expulsive period ranges from about 20-30 minutes in the

multiparous to one hour in the nulliparous.

Following the expulsive phase, there is the period of the afterbirth, which can be natural or artificial. Thus occurs the expulsion or extraction of the fetal appendages of the maternal organism, in a uniform manner and unrelated to the mechanical modalities of expulsion of the foetus. The last phase is defined as post-partum, a period which indicates the 2 hours following the expulsion of the placenta. The woman will have to be supervised and her general state will have to be checked, as for blood loss, contraction and retraction of the uterus.

Diagnostic methods for monitoring in pregnancy

A delicate period such as that of pregnancy needs the right attention from the specialist medical staff, to ensure the health of the mother and the unborn child through an appropriate number of checks and tests to diagnose any complications, with the aim of minimizing maternal and perinatal mortality. The World Health Organization (WHO) *(Asatiani et al., 2010)* defines antenatal care programs in this regard, to guarantee the necessary medical services both during pregnancy and during labour and delivery. They also include the education of the mother, partner or family in transitioning to parenting and encouraging a healthy lifestyle, to promote the health of the baby even after birth.

The woman must be aware of all the risks can be faced and of the behaviours to avoid during pregnancy, for the well-being of herself and of the foetus, for example the type of diet to be followed and the damage resulting from alcohol or smoking. It is therefore necessary that the woman periodically undergoes check-ups, with variable frequency according to the cases, generally on a monthly basis up to the 28th week, every two weeks until the 36th and weekly until delivery. During the first visit *(Pescetto et al., 1989)*, in which the pregnancy is diagnosed, and in the following ones, the woman will therefore be subjected to a series of exams, specifically:

- Inspection: some signs of presumption of pregnancy are confirmed, verifying the presence of skin and mammary changes, the increase in volume of the abdomen and the existence of leukorrhea gravidarum. The inspection is completed by measuring the woman's height and weight.
- Palpation: usually performed with the patient supine, leaning on a rigid surface, it allows to appreciate the variation of the shape of the uterus, the position of the uterine fundus, the situation in which the foetus is found (longitudinal, transverse or oblique) and the characters of the head. It is performed through Leopold's four manoeuvres.

- Listening: the instrument used is an obstetric stethoscope with a wide support mouth, in wood or metal, which allows to detect the sounds and noises produced by the foetus, such as fetal heartbeat, umbilical cord murmur and any movements of the foetus, and from the mother, i.e., aortic pulsation, placental murmur (a breath synchronous to the maternal pulsation, due to the swirling flow of blood in the placental circulation) and noises caused from intestinal activity. Listening takes place in a silent environment, with the help of a stopwatch and take the patient's pulse, to distinguish her heartbeat from that of the foetus.
- Exploration: usually done vaginally, using both hands, one of which is placed on the abdomen, it pushes the uterus towards the probing fingers. It should be performed in labour or when there is the suspicion of rupture of the membranes and allows to evaluate the shape and consistency of the uterus, the position of the foetus and, near the end of pregnancy, allows to evaluate approximately the imminence of childbirth.
- Laboratory tests: at the beginning of pregnancy, tests for the blood group determination (with Rh factor determination), azotaemia, glycaemia, cholesterol, triglycerides, transaminases, bilirubin, lactic dehydrogenase, phosphatase, alkaline, serological reactions for toxoplasmosis, haemoglobin rate and haematocrit value, tests for any infections, especially genital infections, such as chlamydia or gonorrhoea and urine tests, for the detection of proteinuria, glycosuria andbacteriuria, are conducted; it is advisable to repeat these last tests every 10-15 days.
- Blood pressure measurement: it is detected by listening or with an oscillometer, with the patient seated, after an adequate period of rest. It is good that it is measured every 8-10 days and that it remains within the limit values of 140 mmHg for systolic and 90 mmHg for diastolic.
- Diagnosis by ultrasound: diagnostic techniques of this type include echography, echotomography and ultrasonography. Ultrasound uses diffused reflected energy by the structures under investigation; ultrasound takes advantage of the mechanical energy of sound, but it adopts frequencies much higher than those perceivable by the human ear; instead, ultrasonic energy can be continuous or impulsive: the first case allows the use of a technique based on the Doppler effect, the second allows to create an image by reflection.

In the obstetric field, the Doppler effect lends itself very well to the study of heart pulsation of the foetus and blood flow in the great maternal and fetal vessels, as this physical phenomenon can be used to study moving structures and is based on the observation that when a pulse beam encounters a moving body, the frequency of echoes reflected in each single wave is modified according to the movement itself with respect to the transducer. In the Doppler effect devices, there are separate transducers for the emission of vibrations and for the collection of return

echoes. In devices intended for the early detection of fetal heartbeat, the two transducers are paired, and the beam divergence angle of ultrasound is quite small, allowing an approximate localization of the origin of the signal and reducing disturbing noises. Instead, in the devices intended for processing continuous fetal heartbeat, we tend to use a more divergent beam of rays, so to include a greater volume of tissue and to ensure that the registration does not stop with the movements of the woman or the foetus. Ultrasonography using Doppler offers the possibility, during pregnancy, to evaluate the fetal-placental blood flow and the maternal blood flow to the intervillous space (Doppler flowmetry).

The flow of maternal blood to the uterus is visualized by studying it in the branches of the uterine artery and it can thus evaluate the quantity of blood and the speed of the flow entering the intervillous space. To quantify the volume of blood and the speed with which it circulates in the vessels of the funiculus, we usually use a technique that displays the waveform and compares the maximum level of velocity achieved during systole of the fetal heart in the umbilical artery with the minimum velocity that occurs at the end of diastole.

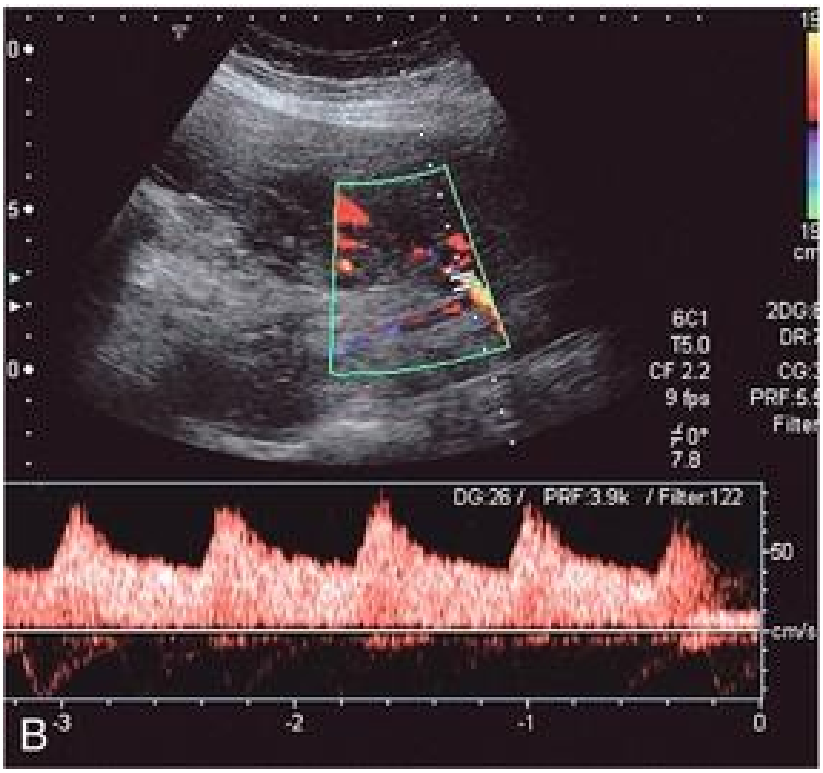

Figure 5. Normal uterine artery flow in the early third trimester demonstrating high diastolic flow. (Clinical Applications of Doppler Ultrasound in Obstetrics, 2015)

Finally, the Doppler effect is also applied in Cardiotocography[2], for monitoring and assessing the health of the foetus, especially in pregnancies defined at risk.

Regarding the use of ultrasound to obtain ultrasound images, the ultrasonic waves are emitted in successive pulses. When the vibrations encounter an obstacle to their propagation, some of the energy comes reflected and part continues. The reflected ultrasonic waves are picked up by the same transducer, which emitted the original impulses, then the echo waves are transformed in electrical signals of intensity proportional to the captured energy. The time it takes for wave propagation is proportional to the distance between a given structure and the point of origin of the waves themselves. It is therefore possible to process both the intensity of the electrical signals and the time it takes for the echoes to form in order to create an image of the structures encountered by the ultrasonic wave beam. Images can be of one-dimensional type, but they can also be transformed to represent the movement of certain structures as a function of time.

They can finally be of two-dimensional type and in this case, they are obtained from probes of various kind that provide a complex of signals from which, with appropriate electronic processing and digital analog conversion, the two-dimensional image of the investigated section is created on the screen of the device. The use of the aforementioned images, as well as in routine monitoring, has a relevant utility in the diagnosis of fetal malformations.

- Biochemical evaluations of fetal blood: for the biochemical diagnosis of the stages of fetal suffering, the evaluation of the main parameters for acid-base fetal blood balance (pH, partial pressure of CO_2, excess of bases etc.) need to be performed. The technique consists of visualizing the presented part of the foetus through an endoscopic tube inserted through the cervical canal, from which a small incision is made with a lancet and finally the collection of the small amount of blood that flows from the incision is performed with a capillary, in order to extract up to 0.5 ml of blood. However, the micro-collection can only be performed after spontaneous or artificial breaking of the membranes and therefore only in labour.

A reassuring pH oscillates between 7.30 and 7.25; for higher values and if there are no anomalies in the cardiotocography plot, labour can be allowed to continue, while values below 7.20 indicate a possible risk. As an alternative to this technique, it is possible, with the analogous objective of determining the acid-base state in fetal blood, to take arterial and / or venous blood from the umbilical cord.

[2] Cardiotocography will be further treated in Chapter 2

Table 1. Reference values for pH and base excess (BE) (Danti et al., 2021)

	pH	BE
Normal values	**>7.2**	**<-4mmol/l**
Mild respiratory acidosis	**7.15-7.20**	**>-4 <-8mmol/l**
Modest respiratory acidosis	**7-7.15**	**>-8 <-12mmol/l**
Metabolic acidosis	**<7**	**>-12mmol/l**

Table 2. Apgar scoring system (Nirmala et al., 2015).

Sign	Score		
	1	2	3
Color	Pale blue	Pink body, blue extremities	Completely pink
Reflex irritability	None	Grimace	Vigorous cry
Heart rate	Absent	Slow (<100)	>100
Respiratory effort	Absent	Slow (irregular)	Crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Score interpretation			
Score		Status	
7-10		Normal	
4-6		Moderately depressed	
0-3		Severely depressed	

Finally, after delivery, it is common to conduct an assessment of the state of health of the new-born,associating a score for each parameter, according to the convention of the Apgar index. In particular, heart rate, respiration, muscle tone, reflexes and complexion are taken into account, assigning a value from 0 to 2 to each of them, depending on the circumstances. The sum of those scores reports the presence of a critical new-born, if less than 4, a new-born to be supervised, if from 5 to 6, or a healthy new-born, if 7 to 10.

Risks for the mother

A periodic pregnancy check *(Pescetto et al., 1989)* is essential to ensure not only the best possible outcome itself, but also to prevent or adequately treat any pathologies that can affect women with a higher frequency than in extra-pregnancy conditions.

Starting from the urinary and digestive systems, it is believed that there is a reciprocal relationship between pregnancy and nephropathy, therefore the woman is more exposed to acute renal failure, but also, to urinary infections, due to changes in the excretory urinary tract already towards the end of the first trimester. Diseases of the mouth and teeth, such as gum swelling, are quite common, as well as gastroduodenal ulcers, which often worsen in late pregnancy or early weeks of puerperium, possibly in relation to anxiety-inducing factors; in these cases, solutions with antacids action should be used in moderation or avoided altogether.

Vomiting is quite common, although it is not a real pathology, but rather a common symptom of the state of pregnancy, especially if early, while late vomiting is rarer and almost always linked to a pathology. The enlargement of the uterus can sometimes create the conditions for an intestinal mechanical occlusion to occur, usually secondary to the displacement of intestinal loops, followed by the formation of an intussusception. When the occlusion arises without any apparent cause, it is spoken of idiopathic ileus gravidium, which is however very rare. Pregnancy can affect liver disease, in fact, it can be the immediate cause of a liver disease or be the triggering factor that reveals one latent.

In the context of cardiovascular diseases, the cardiocirculatory changes in pregnancy that can affect the course of a cardiopathy are the tendency to tachycardia and increased cardiac volume-minute, which reach the maximum value already towards the 12^{th} or 14^{th} week, the increase of circulating blood mass, the development of the placental circulation, the tendency to hydrosaline retention, the increased oxygen consumption, the rapid changes in the venous return of blood to the heart, of cardiac volume-minute, of peripheral resistance in relation to variations in position of the pregnant woman. Even in the case of a healthy pregnancy, the already mentioned changes are often responsible for the so-called "cardiorespiratory syndrome of pregnancy", characterized by tachypnoea, easy fatigue and reduced effort tolerance. The risk increases in labour, due the anxious state of the patient and the work done by the uterine muscle, and in case of heart disease the risk of maternal mortality is present, but fortunately it can be greatly reduced, through adequate supervision and assistance. Another complication of pregnancy can be hypertension, whether it pre-exists at the beginning of gestation, or especially when arises during the second or third trimester and must be considered among the maternal

diseases that cause perinatal mortality and morbidity and, more rarely, maternal mortality. In case of mild hypertension, with systolic blood pressure values below 160 mmHg, pregnancy is usually well tolerated.

Greater risks arise when there are complications and a detachment of the placenta occurs untimely, up to talk of complications such as maternal death for cerebral haemorrhage, bilateral cortical necrosis of the kidneys and disseminated intravascular coagulation haemorrhages.

Another very frightening complication in obstetrics is pulmonary embolism, caused by emboli that originate mainly from the pelvic and lower limb veins. Although serious cases are in decline, it is still one of the most important causes of maternal mortality, together with haemorrhagic and infectious complications and heart disease.

In cases in which an infectious disease occurs during pregnancy, the doctor's considerations concern the possibility that pregnancy can cause an aggravation of the disease, that the disease can influence the evolution of pregnancy, even with repercussions on the foetus, or that disease and pregnancy do not affect each other. Generally, it can be said that there is some certainty predisposition in pregnant women to renal, hepatic and respiratory complications and that if the infection leads to strong temperature rises, it is possible to have an abortive or preterm labour, for which it is necessary to treat the woman paying attention to the action that the drug may have on the baby.

In the endocrine-metabolic field one of the most relevant diseases in obstetrics is diabetes, due to the consequences to which it can lead and above all because careful and timely therapy can reduce, if not cancel out, the negative effects on the mother and the foetus. For these reasons, all pregnant women who fall within the category of potential or latent diabetes must be subjected to appropriate tests immediately after the first prenatal visit and again between 28th and 32nd week.

Risks for the foetus

The manifestation of pathologies *(Pescetto et al., 1989)* favoured by the state of pregnancy or diseases from which the mother suffered previously, but that the pregnancy contributed to aggravate, together with any incorrect or careless behaviours of the woman, can expose the foetus to significant risks.

The use of certain drugs and the administration of certain vaccines, for example, are related to possible harmful reactions, such as fever and anaphylactic shock, which can cause abortion or preterm birth.

Exposure to ionizing radiation can damage the baby in several ways: irradiation in uterus can cause death, irradiation of the embryo can cause severe malformations of the central nervous system, fetal irradiation can lead to injuries of various kinds, such as alopecia, atrophy of the most exposed skin areas and hydrocephalus.

Maternal heart diseases are, in the most serious cases, linked to perinatal mortality, although deaths have declined significantly in the last decades; as regards the effects of cardio vascular diseases on the foetus, it should be noted that the heart disease carry an increased risk of preterm birth and delayed growth of the foetus. Even in the case of maternal hypertension, perinatal mortality is 6-15% if the arterial pressure is equal to or less than 160/110 mmHg, but the foetus or new-born may also die from consequences of antihypertensive and sedative therapy, which can aggravate the already deficient uterus- placental circulation and blocks the ability of the foetus to react to hypoxia[3] by means of a compensatory tachycardia and preferential redistribution of blood to vital areas. Neonatal morbidity is also high, although difficult to express in precise figures; the new-born is often premature due to spontaneous or induced preterm birth as there were obvious signs of fetal distress.

The presence of infections in the mother can infect the baby both during pregnancy and during delivery and carries a variable risk to the foetus, which does not necessarily depend on the severity of the maternal symptoms, as sometimes the harmful consequences on the embryo or foetus are few or absent. Infection is also not synonymous with disease, on the contrary the percentage of children who are sick is almost always rather low compared to the infected; however, cases vary according to infections and related therapies.

Focusing on the effects of maternal diabetes on the foetus, we can define fetopathy and diabetic embryopathy. Fetal death with little or no warning signs is one of the best-known manifestations of diabetic fetopathy, while diabetic embryopathy predicts a greater tendency to abortion in the most severe diabetes classes. It has also been shown that there is a notable incidence of fetal malformations, which increases proceeding from the less severe class to that of greater severity. Damage to the foetus with risk of intrauterine death, asymmetric type retarded growth, preterm birth and malformations, is not only due to the toxic effect of hyperglycaemia, but also to the equally toxic one of a series of metabolites that the diabetic produces, if not perfectly controlled from the metabolic point of view. This control can only be achieved if the woman reaches pregnancy already in optimal conditions; the task of the obstetrician is therefore addressed to identify cases with risk of malformation and those with risk of intrauterine death from the very

[3] Hypoxia is the reduction of oxygen in the peripheral organs, as a consequence of a process of centralization of the flow aimed at preserving the noble organs (heart, central nervous system)

beginning, to perform a perfect glycaemic control in the appropriate period.

One of the most significant dangers to the health of the foetus, which almost always occurs as a complication during labour or the days immediately preceding it, is acute fetal suffering, also called asphyxia[4]. All conditions that interfere with the transport of oxygen from the atmosphere to the fetal tissues can cause asphyxiated fetal suffering. Very schematically, we can talk about:

- maternal causes, such as cardiopulmonary diseases, anaemia, compression of the vena cava and of the aorta by the pregnant uterus.
- placental causes, for example all conditions of impaired blood perfusion of the intervillous spaces or fetal capillaries of the villi.
- funicular causes, such as turns of the umbilical cord around the foetus' neck, knots or prolapse of the funiculus.
- fetal causes, such as fetal cardiovascular insufficiency

In clinical practice, it is not essential to make a diagnosis of the various causal factors; what matters is promptly recognizing the existence of the condition of asphyxiated fetal suffering and free the foetus from a life-threatening condition. The slowing of respiratory exchanges between mother and foetus involves first of all a reduction in the oxygenation of the fetal blood and an accumulation of carbon dioxide in it; moreover, the reduced supply of oxygen influences the establishment of a predominantly anaerobic metabolism, resulting in an increased production of acid metabolites, such as lactic acid, which accumulate and cannot be metabolized or disposed of through the placenta. The result is a change in blood pH, which can be measured by biochemical evaluation of fetal blood and reflects within certain limits the severity of the situation. Hypoxia and acidosis[5] obviously also involve the functionality of all fetal organs and tissues, since, as a consequence of the asphyxiated state, compensatory mechanisms come into play, determining preferential dosing toward the organs of greatest importance for the survival of the foetus, like the liver, brain and heart, at the expense of other organs such as the intestine. Despite the relative protection offered by the phenomena of centralization of the circulation, the fetal heart activity presents some fairly typical modifications that form the basis of the clinical analysis of fetal suffering. The earliest alterations cannot be audibly detected but require the continuous instrumental recording of the fetal heart rate[6] by means of the cardiotocograph.

[4] Asphyxia is the reduction of oxygen in the central organs

[5] Acidosis is an accumulation of acids in the body, not adequately compensated by as many basic substances.

[6] The fetal heart rate is calculated at each recorded occurrence of a fetal heartbeat. It represents one of the most interestin g fetal cardiac indexes and it is generally expressed in beats per minute (bpm). It is calculated on the basis of the length of the RR

Chapter 2

Cardiotocography

Cardiotocography (CTG) *(Agostinelli et al., 2016)* was introduced in 1958 to assess the state of health of the foetus during labour. It is possible to find it defined with the synonym "electronic fetal monitoring" *(Alfirevic et al., 2008)*, even though with this term we do not include the uterine contraction monitoring, which is instead performed by a cardiotocograph. In fact, the CTG consists of a simultaneous detection of fetal heart rate and uterine contractions, by means of two distinct sensors, specifically a Doppler ultrasound probe for heart rate and a pressure transducer for the detection of contractions.

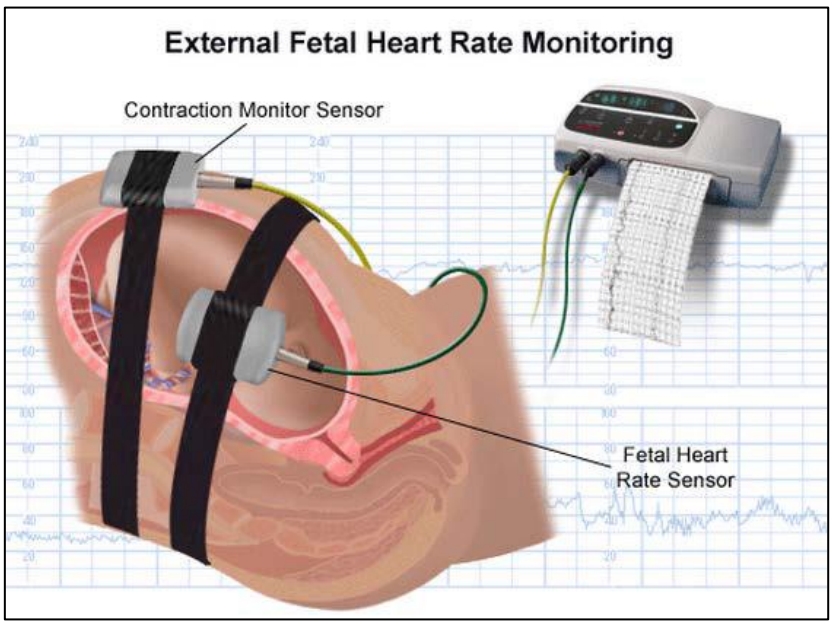

Figure 6. An external fetal cardiotocography (CTG) monitor (Abdulhay et al., 2014)

The CTG *(Prior et al., 2018)* is mainly used for fetal monitoring in the intra-partum period, but also in the antenatal phase, especially in growth restricted foetuses, who are more incline to abnormalities of fetal heart rate rhythm. Generally, an external monitoring is performed during labour *(Alfirevic et al., 2008)*, when it is asked to the mother to wear a sort of belt, with the disadvantage to reduce her mobility. An alternative is to perform an internal CTG, by attaching

time interval, i.e., the time delay between two heart beats, usually identified with the peak of the R wave of the QRS segment on the electrocardiographic trace (ECG). The fetal heart rate depends on the intrinsic rhythmicity of the myocardium and is subject to the control of the autonomic nervous system (ANS) centers

the electrode directly on the baby's presenting part, usually the head. This procedure also restricts woman's mobility and requires the rupture of the membranes, so it can only be performed during labour.

The main reason for using the CTG *(Alsaggaf et al., 2020)* in routine clinical practice is the possibility, through the results of CTG tests, of anticipate the actions of the sympathetic and parasympathetic nervous systems and thus determine an eventual state of poor oxygenation of the foetus. Tracking standards vary from country to country, generally the recording scale is 1 cm / min, with sampling frequency at 4 Hz, that is, four samples taken every second.

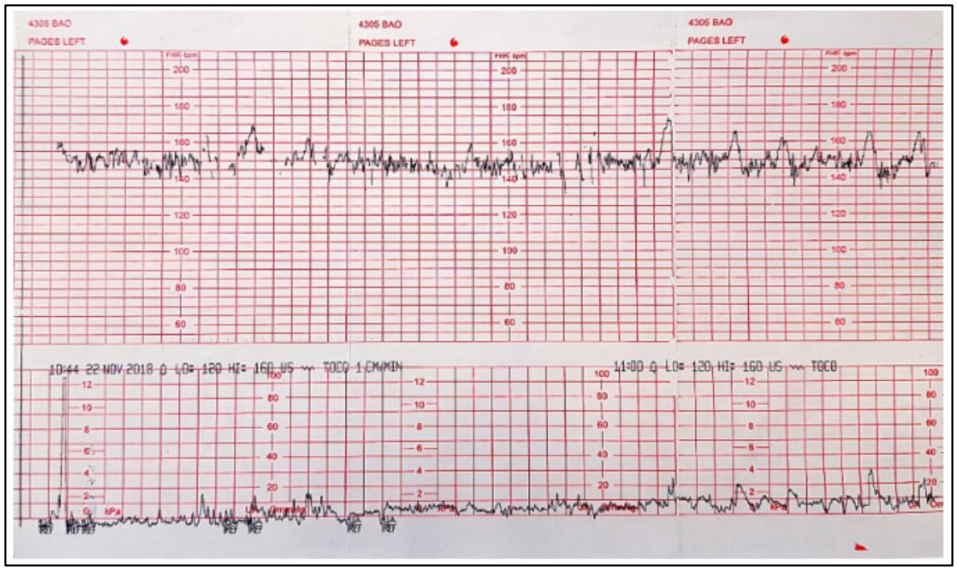

Figure 7. An example of CTG tracing (Cömert et al., 2019).

Each square on the horizontal axis corresponds to 30 sec whereas each square on the vertical axis matches 5 bpm for FHR and 10 mmHg for UC, respectively. The FHR and UC in the vertical axes are limited in the range of 50 and 210 bpm and 0 and 100 mmHg, respectively.

The CTG trace reading is performed traditionally by the medical / obstetric staff, therefore it is linked to a strong subjectivity. To reduce variability between observers, guidelines have been introduced to support the assessment objective of CTG traces and the clinical management of specific CTG patterns, such as baseline, variability, accelerations, decelerations, sinusoidal trend, pseudo-sinusoidal trend and contractions. Specifically, these are the standards introduced by the International Federation of Gynecology and Obstetrics (FIGO), National Institute for Health and Care Excellence (NICE) and American College of Obstetrics and Gynecology (ACOG).

Despite this, errors due to the inter- and intra-staff variability and reduced reproducibility of

CTG interpretation remain not negligible. To face these problems, computerized systems that use advanced signal processing and machine learning are an attractive approach to quantify the temporal dynamics of the CTG traces.

The cardiotocograph

Characteristics of the instrument

Cardiotocographic monitoring (CTG) is performed by means of a device called cardiotocograph *(User Manual FC700, 2020)*, which allows electronic monitoring of the fetal heart rate (frequency, variability, accelerations, decelerations) and uterine contractions (number, duration, basal tone). The cardiotocograph radiates and detects the Doppler signal returning from the heart of the foetus. It analyses this signal, displays the frequency of the fetal heartbeat and plays the sound of the fetal heart. It measures the intensity of uterine contractions (UC) of a pregnant woman with a pressure sensor and displays numerical values, records fetal heart rate (FHR), fetal movements and values relating to the intensity of uterine contractions.
The detected signal can be printed graphically on generic fax paper or thermal paper for fetal monitors. The system usually consists of a set of components, in addition to the main body of the cardiotocograph, as the Doppler probe, UC contraction probe, event detector button, printer paper, power adapter, power cable, ultrasound gel, probe strap. This equipment complies with class I, according to IEC / 60601-1 (Electrical Safety of medical equipment). Ground connection points connect to the separate adapter, as the instrument does not have its own ground connection points. The configuration of the main body provides a control panel, a LED screen on which it is possible to read the numerical values of the detected parameters and the printer door, for printing. The printing method is through thermal head printer, with speed of 1, 2, 3 cm / min and resolution of 8 (vertical) / 10 (horizontal) dot / mm. On the side, there are the connectors for Doppler and UC contractions probes. The CTG analysis of the results is printed every ten minutes.
The values of interest are the average baseline of the FHR, which is the average number of fetal heart rate baselines during the analysis period; the number and frequency of UC; the value and frequency of acceleration and deceleration per hour; the delay and advance of deceleration during the deceleration phase; variable decelerations; possible moderate (> 160 bpm) or severe (> 190 bpm) tachycardias and moderate (<110 bpm) or severe (< 90 bpm) bradycardias.
The appliance must be installed in environments with temperatures between 10 ° C and 40 ° C,

checking the correct connection of the probe cable and not connecting other equipment to the same power supply. The entrance of the adapter is in AC from 100V to 250V. The instrument also has an internal lithium battery.

Techniques for recording the track

The recording *(User Manual FC700, 2020)* of the track consists, as the first operation to be performed, in the placing of the desired settings on the cardiotocograph. Once plugged into the power supply and put in function, these settings can be checked and adjusted.

The Doppler and UC contraction probes are fixed with belts to the abdomen of the pregnant woman, to whom an event detection button is given, and she will press it whenever she senses a fetal movement. The recording of the fetal heartbeat starts manually, by pressing the "record" button, when the signal is clear and with an appropriately adjusted volume. The quality of the performed monitoring depends considerably on the positioning of the two probes on the mother's body.

For the measurement of fetal heart rate, the Doppler technique is used, detecting the return ultrasound signal of the fetal heartbeat; the ultrasound signal has a frequency of 1.0 MHz, the measurement range is 50-240 bpm, with accuracy ± 1 bpm and ultrasound sensitivity of 95dB at 150mm. It is necessary to minimize the interference by applying an adequate amount of gel on the Doppler probe and eliminating any air pockets. A badly connected probe is signalled by an audible alarm, in addition to the fact that no FHR value will appear on the monitor. The belt should be placed at the height of the pregnant woman's wrist, the probe on the abdomen, for finding the back of the foetus by touching the abdomen itself. If the foetus were in a lateral position, the probe should be placed as in Fig.8.

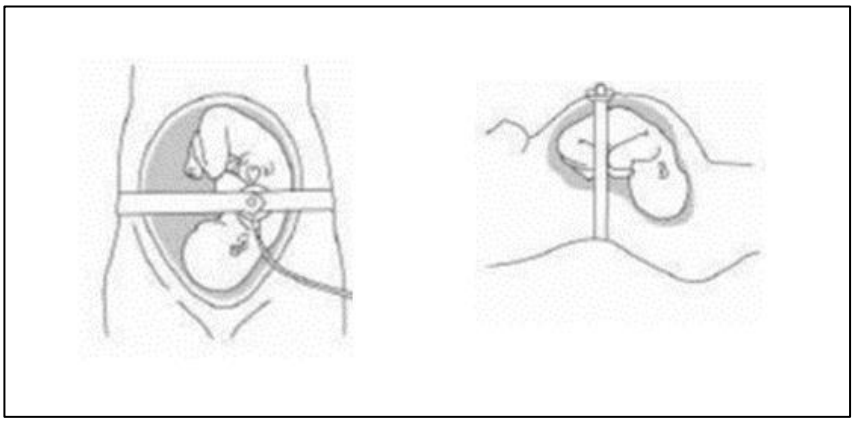

Figure 8. Position of the probe on the abdomen of the pregnant woman (User Manual FC700, 2020)

If the probes were placed on the chest rather than on the back of the foetus, a clear signal would not be obtained; to improve the acquisition it is possible to move the Doppler probe to find the point where the sound of the fetal heartbeat is the loudest and clearest. It is good to fix the probe cable close to the head of the pregnant woman, in order to prevent it from being damaged or moved too much.

The measurement of the uterine contractions takes place by applying an external pressure sensor (external transducer with strain gauge), which measures the pressure variations relative to the UC and records these contractions. Also in this case, an acoustic signal warns in case of wrong connection and no UC value appears on monitor. The belt needs to be located behind the back of the pregnant woman, the probe is positioned about 10 cm above the navel or at the point where the pregnant woman felt a contraction.

Fetal cardiotocographic monitoring

Objectives of fetal monitoring

The main goal of fetal monitoring *(Yli et al., 2016)*, especially in the phase of labour, is to detect complications, even unexpected ones, in order to intervene in the best possible way to ensure the health of both the child and the mother. However, monitoring should not be considered as a substitute for clinical judgment, but rather as an aid to medical personnel. Specifically, intrapartum monitoring has the purpose of identifying inadequately oxygenated foetuses to try to resolve promptly this problem or, on the contrary, to avoid unnecessary obstetric interventions.

During fetal life, the oxygen supply depends on the maternal circulation and respiration, on placental perfusion, on gas exchanges through the placenta, on the umbilical and fetal circulation. In case that one of these systems is altered, a drop in oxygen concentration can occur in fetal arterial blood (hypoxemia)[7], subsequently at the tissue level (hypoxia), and finally at the level of the central organs (asphyxia). Some degree of hypoxemia occurs in almost all foetuses during labour *(ACOG Practice Bulletin, 2009)*; the onset of a state of hypoxia, with subsequent possible metabolic acidosis, instead, depends both on the entity, duration and repetitiveness of the events responsible for a reduced contribution of fetal oxygen, and from the metabolic reserves of each foetus at the onset of labour. Only after the nullification of the

[7] Hypoxemia is the initial phase of reduced oxygen supply, and it is characterized by the presence of reduced oxygen saturation in arterial blood. The foetus adapts by optimizing the oxygen uptake processes and reducing its movements to save energy

compensation mechanisms and the exhaustion of reserves, hypoxic fetal pathology occurs.
When a picture of hypoxia is established, the cellular production of energy can still be maintained for a limited period of time by the anaerobic metabolism; however, this process produces about 19 times less energy than the aerobic metabolism and causes an accumulation of lactic acid inside the cell, with subsequent passage into the extracellular environment and into the fetal circulation. The increased concentration of hydrogen ions of intracellular origin in the fetal circulation is called metabolic acidosis, a process directly proportional to the concentration of hydrogen ions in the tissues. In clinical practice the tissue oxygen concentration cannot be quantified, therefore parameters which allow to determine a state of acidosis are evaluated.
The most used method involves a sample of umbilical cord blood *(Ross et al., 2002)*, from which it is verified that the pH and base excess (BE) are within the ranges of normality; a pH below 7 and an excess of bases> -12 mmol / l are indicators of properly said metabolic acidosis. Conditions of this type can impair cell function, causing damage to internal organs, cerebral palsy and putting the foetus at risk of death. Hypoxia can also be caused by events specific to childbirth, for example the uterine contractions itself compress the maternal blood vessels within the myometrium, decreasing placental perfusion and temporarily reducing gas exchanges with the foetus. The frequency, duration and intensity of the uterine contractions are therefore determining factors to ensure adequate fetal oxygenation.
Particular interest should be given to the intervals of contractions *(Peebles et al., 1994)*, which in the case of spontaneous labour are of about 120 s, 3-4 contractions in 10 minutes, while in induced labour the interval increases to about 138 s. Excessive uterine contractile activity is often responsible for a reduced oxygenation and therefore should be avoided. Adequate intrapartum fetal monitoring can thus avoid adverse neonatal outcomes from hypoxia and acidosis, as long as it does not cause an increase of unnecessary obstetric interventions, such as operative vaginal deliveries and caesarean sections, with a consequent increase in maternal-fetal risks.

The fetal heart rate

In the context of fetal monitoring, one of the fundamental parameters to be monitored is undoubtedly the fetal heart rate (FHR), detected by cardiotocography. According to the American College of Obstetricians and Gynaecologist (ACOG) *(Morgera),* we can distinguish three types of fetal heart rate:

- FHR of the first type, normal trace, strongly predictive of normal acid-base state; no particular specific action is required.
- FHR of the second type, indeterminate trace, which is not predictive of acid-base equilibrium anomalies and requires continuous surveillance and subsequent re-evaluation.
- FHR of the third type, abnormal tracing, which is associated with alterations in the acid-base balance, at the time of observation. Specific clinical solutions should be considered, for example administering oxygen to the mother, changing position, suspending any stimulation of childbirth, and considering possible maternal hypotension. If the alterations persist, action must be taken quickly upon delivery.

The CTG analysis begins with the evaluation of the basic characteristics of the track, which can be identified thanks to the external monitoring of the FHR and its registration of acceptable quality and clear enough to be the subject of study and detection of any anomalies.

Baseline FHR

The first parameter to consider is the basal FHR *(Ayres-De-Campos et al., 2015)*, i.e., the mean value of a segment of FHR estimated over a period of 10 minutes, expressed in beats per minute (bpm).

Normal values are between 110 and 160 bpm, preterm foetuses tend to have values close to the upper limit of this range, vice versa the post-term ones tend towards the lower limit.

Tachycardia is defined as a baseline value greater than 160 bpm for a duration greater than 10 minutes. It can be caused by maternal pyrexia, of extrauterine origin or associated with an intrauterine infection. Epidural analgesia can also be a cause of increased maternal temperature, resulting in fetal tachycardia. Other conditions that can lead to tachycardia are the catecholamine secretions during the early stages of non-acute fetal hypoxemia, administration of Beta-agonist drugs (salbutamol, ritrodrin, fenoterol) or fetal arrhythmias such as supraventricular tachycardia and atrial fibrillation.

Bradycardia is characterized by a baseline value below 110 bpm for a time greater than 10 minutes. Values between 100 and 110 bpm can occur in normal foetuses, especially in post term pregnancies. The main causes of bradycardia include maternal hypothermia, the administration of beta-blockers and fetal arrhythmias such as atrioventricular blocks.

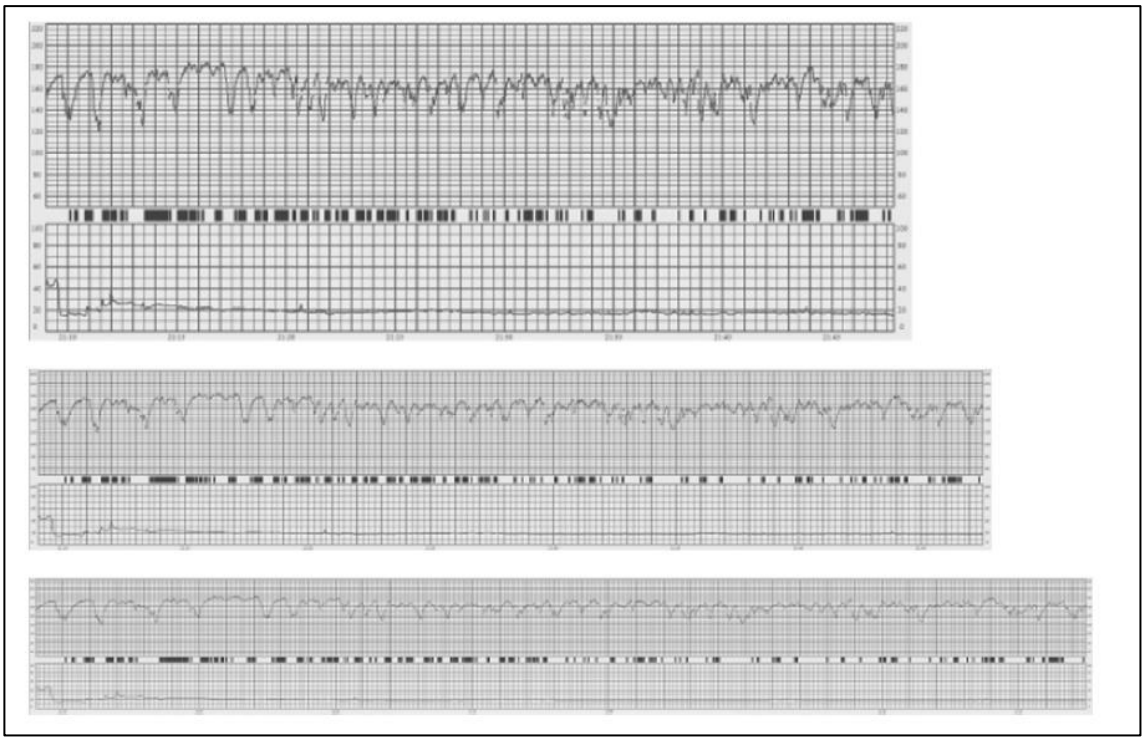

Figure 9. Fetal behavioural state of active wakefulness. External fetal heart rate monitoring (Ayres-De-Campos et al., 2015)

Variability

The term variability *(Ayres-De-Campos et al., 2015)* refers to the oscillations in the FHR signal, evaluated in an average bandwidth of the signal in one-minute segments.

Normal variability has an amplitude bandwidth of between 5 and 25 bpm.

The reduced variability corresponds to a bandwidth of less than 5 bpm in width for a time greater than 50 minutes in segments at FHR baseline or for more than three minutes during degenerations. This condition can occur due to hypoxia or acidosis of the central nervous system, resulting in decreased sympathetic and para sympathetic activity, but it can also depend on previous infections, brain injuries and other factors. In general, the variability assumes lower than normal values during deep sleep conditions, but amplitude rarely drops under 5 beats per minute.

On the other hand, the increased variability corresponds to a bandwidth value higher than 25 bpm for more than 30 minutes. This condition is also called *jumping pattern* and it is still object of study, but it would seem related to recurrent decelerations, when acidosis evolves very rapidly. It is presumed to be caused by instability or hyperactivity of the autonomic system of the foetus.

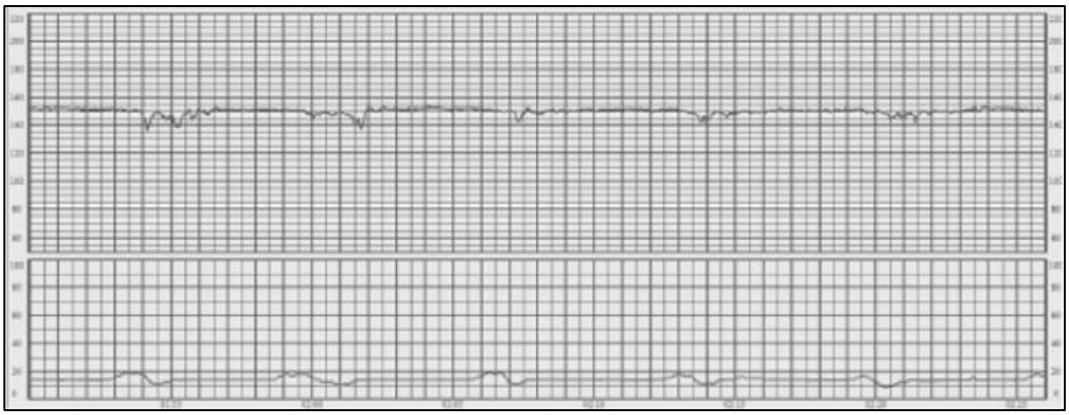

Figure 10. Reduced variability. External fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

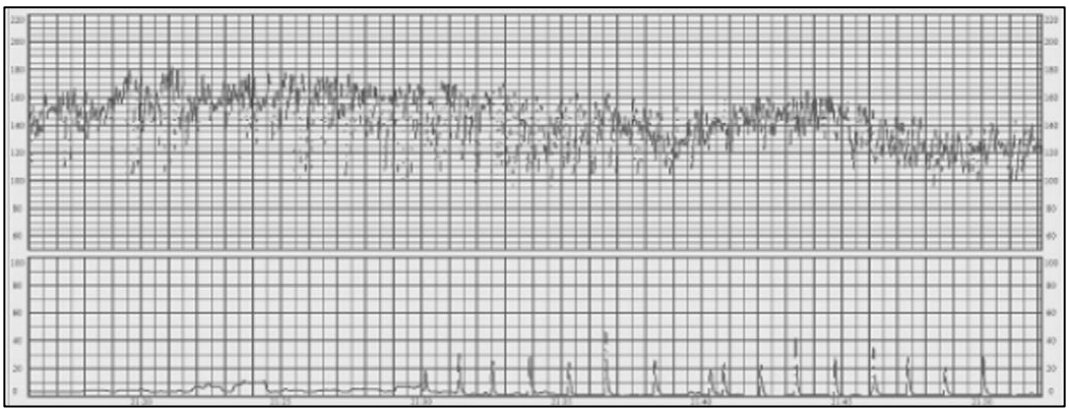

Figure 11. Increased variability: saltatory pattern. Internal fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

Accelerations and decelerations

Acceleration *(Ayres-De-Campos et al., 2015)* refers to a sharp increase in the fetal heart rate above the baseline, more than 15 bpm in amplitude and lasting more than 15 seconds but less than 10 minutes. They often coincide with fetal movements and are a symptom of a correct neurological response of the foetus, which is therefore not in a state of hypoxia. In the first 32 weeks of gestation their amplitude and frequency may be lower; later, when behavioural states appear, the accelerations are rare in the deep sleep phases of the foetus, which usually last around 50 minutes. The absence of accelerations in an intrapartum cardiotocographic trace is unlikely to indicate hypoxia / acidosis, while the correspondence between accelerations and uterine contractions could indicate an erroneous recording of the maternal heartbeat, as the FHR usually decelerates during contractions, while the maternal heart rate increases.

Decelerations *(Ayres-De-Campos et al., 2015)*, on the other hand, are decreases in FHR below

baseline, of more than 15 bpm in amplitude and for a duration greater than 15 seconds.
They are classified into four types:

- Early decelerations: they are shallow decelerations, of short duration, with normal variability and coincidence with contractions. They are believed to be caused by the compression of the fetal head and are not indicative of fetal hypoxia / acidosis.
- Variable decelerations: they present a rapid decline, good variability, rapid recovery of basal line, shape, size and relationship with the variable uterine contractions. They constitute the majority of decelerations in labour and translate a response, mediated by baroreceptors, to the increase in blood pressure, as it happens with a compression of the umbilical cord. They are rarely related to severe degrees of fetal hypoxia, unless they evolve into components such as the U-shape (typical of late decelerations), reduced variability and / or duration greater than three minutes per every single deceleration.

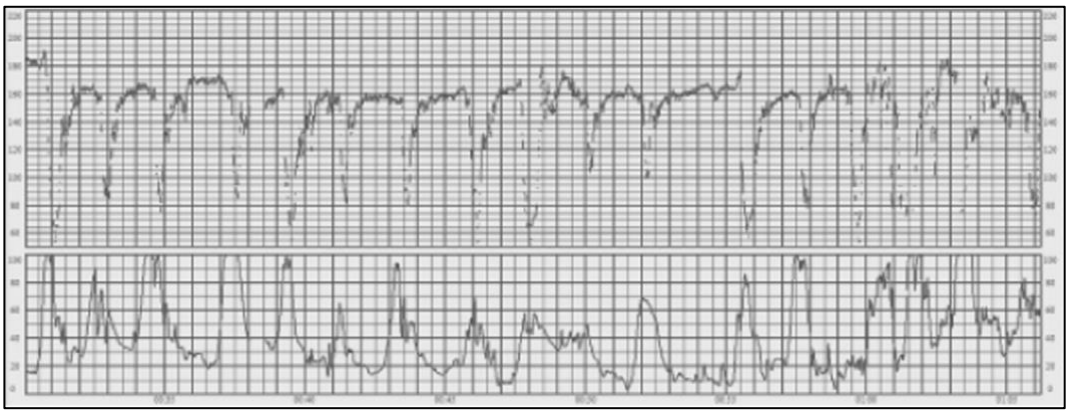

Figure 12.Variable decelerations. I*nternal fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)*

- Late decelerations: their onset is gradual, as is the return to baseline, and the variability is reduced. The beginning and the gradual return to the baseline are defined as a time greater than 30 seconds between the start / end of the deceleration and its nadir. In a trace in which uterine contractions are adequately monitored, the late decelerations begin more than 20 seconds after the start of the contraction, the nadir follows the peak of the contraction and the return to the baseline occurs after the end of contraction. These decelerations indicate a response mediated by chemoreceptors to fetal hypoxemia. In the presence of a path without accelerations and reduced variability, the definition of late decelerations includes even those with an amplitude of 10-15 bpm.

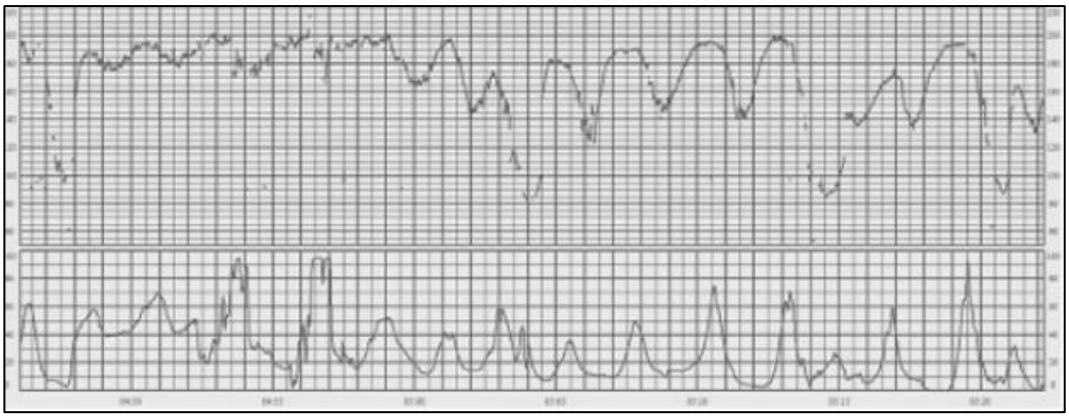

Figure 13. Late decelerations. External fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

- Prolonged decelerations: their duration exceeds three minutes. They are probably related to a response mediated by chemoreceptors and therefore indicate hypoxemia. Decelerations greater than 5 minutes with an FHR maintained below 80 bpm and reduced variability are frequently associated with acute hypoxia and require emergency intervention.

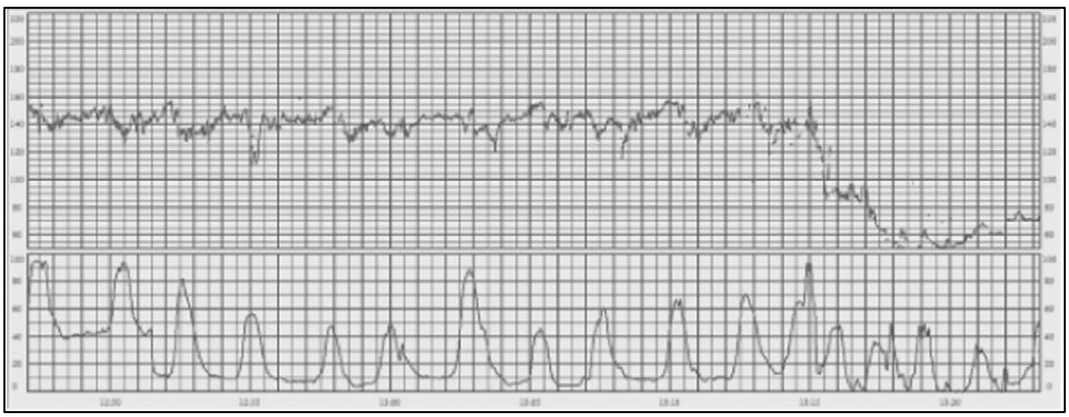

Figure 14. Prolonged decelerations. External fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

Sinusoidal and pseudo sinusoidal patterns

With the definition of sinusoidal pattern *(Ayres-De-Campos et al., 2015),* we mean a regular and undulatory signal, similar to a sinusoidal wave, with an amplitude of 5-15 bpm and a frequency of 3-5 cycles per minute. It lasts more than 30 minutes and coincides with the absence of accelerations. The pathophysiological basis of the pattern is not yet fully understood but is considered to be related to severe fetal anaemia, as in anti-autoimmunization D, fetal-maternal haemorrhage, twin-to-twin transfusion syndrome and rupture of vasa previa (blood vessels blood migrated out of the umbilical cord), as well as cases of acute fetal hypoxia, infections,

cardiac malformations, hydrocephalus and gastroschisis.

Similar to the sine pattern, but with a more "serrated" profile, there is the pseudo sinusoidal pattern *(Ayres-De-Campos et al., 2015)*; generally preceded and followed by normal patterns, it rarely exceeds 30 minutes in duration. It is often related to the administration of analgesic to the mother and occurs during periods of fetal sucking and other mouth movements. It is often difficult to distinguish the two tracks, the most characterizing aspect is the short duration of the pseudo sinusoidal, which allows to differentiate it from the sinusoidal.

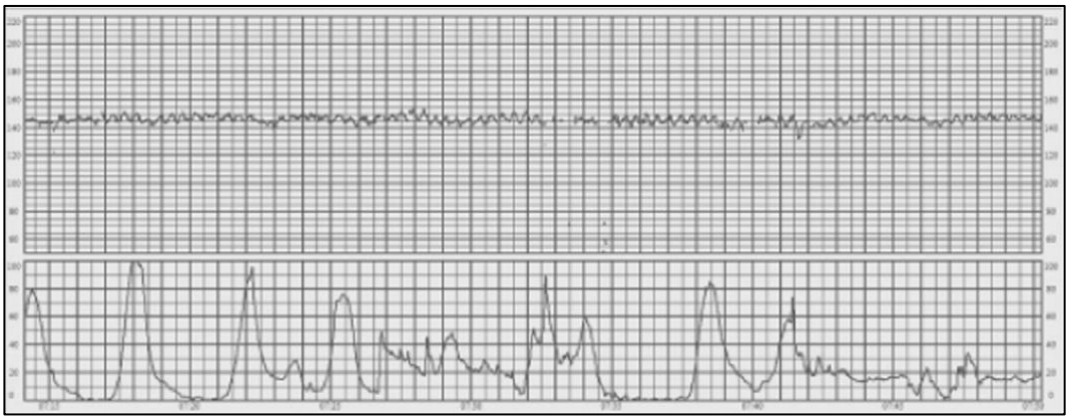

Figure 15. Sinusoidal pattern. External fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

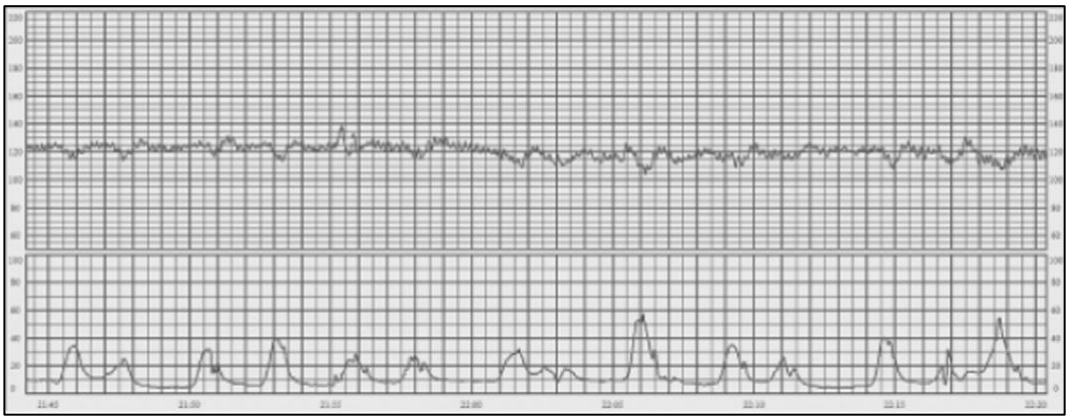

Figure 16. Pseudo sinusoidal pattern. External fetal heart rate monitoring at 1 cm/min (Ayres-De-Campos et al., 2015)

Fetal behaviour

The analysis of fetal behaviour *(Ayres-De-Campos et al., 2015)* refers to the alternation between phases of rest, which is to say deep sleep, lacking eye movement, and active sleep (with rapid eye movements) and phases of wakefulness, divided into quiet wakefulness and active wakefulness (with numerous accelerations). The finding of the alternation between the various

states of activity is an indication of neurological reactivity and the absence of hypoxia / acidosis. Deep sleep can last up to 50 minutes and is associated with a stable baseline, rare accelerations and borderline variability. Active sleep is the most frequent behavioural state and is represented by a moderate number of accelerations and normal variability. The vigil active is rarer, with numerous accelerations, so frequent that it can cause difficulties in estimating baseline, and normal variability. The transition from one pattern to another becomes more evident after 32-34 weeks, as a consequence of the maturation of the central nervous system.

Contractions

The trace that allows the medical staff to analyse the trend of contractions *(Ayres-De-Campos et al., 2015)* is characterized by bell-shaped gradual increases in uterine activity signal, followed by almost symmetrical decreases, with a total duration of 45-120 s. Contractions are the key for the progression of labour, although they compress the vessels of the myometrium and can cause a transient reduction in placental perfusion and compression of the umbilical cord.

An increased intensity and duration of contractions may promote a change in FHR. If the frequency of these contractions is excessive, particularly it exceeds 5 contractions in 10 minutes in two successive 10-minute periods or overall, as an average over a period of 30 minutes, we are talking about tachysystole.

Monitoring of the mother

In the phase of labour, it is essential to monitor the mother as well *(Ayres-De-Campos et al., 2015)*, not only to ascertain her state of health in a particularly delicate phase such as that preceding childbirth, but also for detecting any correspondence between values of the mother and the ones of the foetus. In first place, it is important that the probes are properly placed and that the mother is in a comfortable position but at the same time suitable for optimal detection of the cardiotocographic track.

The maternal supine posture, for example, can cause aorto-caval compression by the uterus, impairing placental perfusion and fetal oxygenation; therefore, prolonged monitoring in this position should be avoided, preferring instead side postures, sitting and orthostatic.

Monitoring of the mother, and in particular the detection of her heart rate (MHR), is especially important in those critical situations in which the woman is in a particular medical condition or if the distinction between fetal and maternal heartbeat is not clear (for example, if the foetus'

heart has stopped). Some cardiotocograph models are already equipped with sensors for simultaneous monitoring of foetus and mother without the need for additional equipment.
Whenever possible and unless it is going to cause excessive discomfort the parturient, simultaneous MHR monitoring is especially useful during a continuous CTG in the second phase of labour, when there are accelerations in correspondence of the contractions or when the maternal heart rate is particularly high. Finally, it can be relevant to keep the patient's body temperature under control, in case of fever or hypothermia that can cause increases or decreases in FHR.

Interpretation of data and clinical interventions

Once a sufficiently clear cardiotocographic trace and the values of reference *(Coletta et al.,2012)* (*Parer.,2007)* , such as baseline FHR, variability, accelerations, decelerations and contractions, are obtained, before to decide if and in what way it is necessary to intervene clinically, the tracing must be classified according to three types (described in *Table 3*). For a correct clinical decision, in addition to the CTG reading, other factors, which could cause the FHR to vary, must be taken into account, for example the gestational age and the administration of certain medications to the mother.
As a general rule, if the foetus maintains a stable and good baseline variability, the risk of hypoxia affecting internal organs remains limited. In the presence of a pathological CTG, with type 2 or 3 tracings, it is necessary to intervene to treat the causes of suspected hypoxia or, in the most serious cases, to conduct the birth as soon as possible with an emergency caesarean section. It is good,however, to conduct a further check, when possible, by taking a fetal scalp sample for the pH determination. The immediate completion of the birth is therefore the last operation to be conducted in those situations in which it is no longer possible to restore the correct oxygenation of the foetus. In less extreme cases, like in type 2 traces, it is usually sufficient to implement corrective measures to report the CTG trace at normal values, although in some situations a persistent type 2 could evolves into type 3, worsening the state of the foetus. The types of treatment vary according to the causes of the reduction fetal oxygenation. One of the most frequent is excessive uterine activity, detectable by CTG and / or palpation of the fundus of the uterus. It can be treated by reducing or stopping the infusion of oxytocin, removing any prostaglandins that may be administered and using beta agonists adrenergic. During the second stage of labour, maternal effort can also contribute to appearance of fetal hypoxia, which can be avoided by briefly asking the patient to stop thrusts.

The supine position of the parturient *(Caldeyro-Barcia et al., 1960)* can cause caval-aortic compression, with consequent reduction of placental perfusion, which can be solved simply by rotation of the patient on the side, to allow normalization of the CTG.

The appearance of fetal tachycardia *(Miyake et al., 2008)* usually follows the presence of maternal fever (temperature over 38 °C) and can be due to extra-uterine or uterine problems, for example chorioamnionitis. It is an infection associated with fever, abdominal pain and foul-smelling amniotic fluid, also related to variations of the CTG trace, such as reduced variability and the presence of decelerations. If the fever is due to chorioamnionitis, it must therefore be treated with antibiotic therapy, otherwise it will be sufficient to administer antipyretic.

Table 3.Cardiotocography classification criteria

	Normal	Suspicious	Pathological
Baseline	110—160 bpm	Lacking at least one characteristic of normality, but with no pathological features	<100 bpm
Variability	5—25 bpm	Lacking at least one characteristic of normality, but with no pathological features	Reduced variability, increased variability, or sinusoidal pattern
Decelerations	No repetitive decelerations	Lacking at least one characteristic of normality, but with no pathological features	Repetitive late or prolonged decelerations during >30 min or 20 min if reduced variability, or one prolonged deceleration with >5 min
Interpretation	Fetus with no hypoxia/acidosis	Fetus with a low probability of having hypoxia/acidosis	Fetus with a high probability of having hypoxia/acidosis
Clinical management	No intervention necessary to improve fetal oxygenation state	Action to correct reversible causes if identified, close monitoring or additional methods to evaluate fetal oxygenation	Immediate action to correct reversible causes, additional methods to evaluate fetal oxygenation or if this is not possible expedite delivery. In acute situations (cord prolapse, uterine rupture, or placental abruption) immediate delivery should be accomplished.

Sudden maternal hypertension *(Simmons er al., 2012)* may result from administration of epidural or spinal analgesia, which can be resolved with an infusion of fluids and / or an intravenous bolus of ephedrine. A widely used practice to improve fetal oxygenation is the administration of oxygen to the patient, a practice indicated only in patients with reduced oxygen saturation levels. Administering intravenous fluids *(Simpson et al., 2005)* is also a very common practice, but also in this case there is no evidence of efficacy for normotensive women. The infusion of intravenous glucose solutions in labour would appear to be a practice to avoid. Maternal hyperglycaemia would in fact cause an increase in maternal and fetal lactate levels with resulting in acidosis. In case of identification of a type 2 or rapidly worsening CTG, the responsible cause should be resolved before evolution to a type 3 path. If with the implemented measures the situation does not regress and the picture continues to worsen, new evaluations are necessary and, in the event of the appearance of pattern type 3, a rapid completion of childbirth is recommended.

Chapter 3

Interpretation of cardiotocographic signals: limits and development of automatic methods

Cardiotocography results to be an efficient but often subjective method, since the evaluation of the signals can be misinterpreted by the medical staff. The development of automated and computerized approaches could represent a breakthrough for a precise and objective evaluation of fetal significant parameters, which could bring a considerable reduction of risks for the newborns during labour and delivery. Research has been focused on this topic since the Seventies, even though the practical application of such software or analysis techniques is still limited. The goal is to find an approach that should overcome the limitations and be accepted worldwide. For this reason, continuous effort is put by the scientific community to propose a solution that could cover all the requested aspects to fulfil a good fetal wellbeing evaluation.
A particular concern is given to the characterization of accelerations and decelerations of the fetal heart rate, being these parameters significant indexes for potential fetal suffering during labour. Over the following reported, different methodologies of cardiotocographic signal analysis can be found in the last years' literature, proving the importance of this subject in medical and biomedical engineering research.

Limits of intrapartum cardiotocography (CTG) interpretation by obstetricians

The golden standard of clinical practice still involves the interpretation of cardiotocographic signals by medical personnel, which introduces a set of limitations. Indeed, while reading a CTG plot, different interpretations could be given by obstetricians of different level of experience and who work in different hospitals and medical centers. According to a study conducted in 2022 by Li et al. *(Li et al., 2022)*, despite a general agreement on interpreting CTG, multiple differences were observed in the identification of some features. Clinical observation generally follows guidelines as FIGO *(Melamed et al., 2021)* and American College of Obstetricians and Gynaecologists (ACOG), with the purpose to have a worldwide accepted method. This allows to define the identification of FHR features as accelerations and decelerations, to predict eventual fetal suffering, as well as risk of acidaemia. The proper analysis of the tracings helps the doctor to decide the intervention with an emergency caesarean.

Considering that, the aims of the Li et al. study were to ascertain the agreement and reliability among obstetricians with different skill levels on the interpretation of non-reassuring intrapartum fetal monitoring, and to explore the accuracy of prediction for neonatal acidaemia. Two groups of experts, respectively from two hospitals (The First Affiliated Hospital of Sun Yat-sen University and Perking University Third Hospital) were asked to review 100 tracings, without knowing markings, neonatal outcome or any other related information. The reviewers were six in total, respectively two with more than 10 years of experience, two with an experience between 5 and 10 years and two with 3 or less years. After analyzing the FHR pattern, the baseline, the variability and the occurrence of accelerations and decelerations, they were asked to predict whether the neonatal acidaemia would occur. Confronting the results, an index named proportion of agreement (Pa) was calculated, showing a satisfying agreement (Pa >0.50) for FHR baseline, accelerations, and late decelerations, especially in the junior group. The agreement of sinusoidal pattern and pattern of FHR tracings was high and similar for the three groups; however, early decelerations were poor. The Pa value of variable decelerations, neonatal acidaemia, and umbilical arterial pH < 7.1 of the senior group were 0.60, 0.62, and 0.98, respectively, which were higher than those of the other two groups. Comparing the two hospitals, reported in *Table 4*, agreement was good except for the early decelerations, which had a Pa of 0.38. Even though early accelerations are less harmful and severe for the result of the outcome, not indicating fetal hypoxia/acidosis *(Melamed et al., 2021)*, the presence of such incongruences in the judgement make it insufficient to meet ideally clinical requirements for "no objection" interpretation for FHR tracings.

Moreover, a particular concern is related to the increasing of caesarean deliveries, since this practice is often applied, even in situations in which it could be avoided. Indeed, not all cases of bradycardia and decelerations in the fetal heart rate are necessarily indexes of fetal suffering and do not need inevitably a caesarean section *(Morgan et al., 2020)*.

Continuous fetal monitoring during labour surely is a safe way to investigate about fetal health, keeping track of any red flag concerning the wellbeing of the foetus himself and the mother, in a way to allow to intervene with emergency procedures in critical cases, as a fetal bradycardia or an excessive variability of the FHR. Nevertheless, there are situations in which the infant is revealed as uncompromised, even after episodes of abnormalities in the tracings, meaning that an emergency caesarean intervention will result in an increasing stress and risk for the mother, more than to be actually useful.

For these reasons, all possible causes of deceleration and bradycardia should be considered and eventually it should be given an attempt to solve them, before applying an emergency

procedure. Therefore, is recommended by several specialists, to apply continuous fetal monitoring up to the way to the operating room. If FHR is restabilized to the healthy values before the arrival to the operation room, the decision to proceed with caesarean delivery can be reconsidered.

Table 4. Inter-observer agreement and reliability between two different hospitals (Li et al., 2022)

Variables	Number of times rated (600 ratings)	Total from all six reviewers		
		Pa (95% *CI*)	Kappa (95% *CI*)	AC1 (95% *CI*)
Baseline		0.93 (0.91,0.96)	0.18 (0.09,0.26)	0.93 (0.90,0.96)
Bradycardia	1	0.00 (0.00,0.00)		
Normal	564	0.96 (0.95,0.98)		
Tachycardia	35	0.46 (0.22,0.67)		
Variability		0.87 (0.83,0.91)	0.05 (−0.04,0.20)	0.86 (0.82,0.9)
Absent	3	0.00 (0.00,0.00)		
Minimal	40	0.10 (0.00,0.23)		
Normal	557	0.93 (0.91,0.95)		
Accelerations		0.58 (0.52,0.63)	0.18 (0.10,0.27)	0.23 (0.11,0.35)
No	212	0.41 (0.32,0.49)		
Yes	388	0.68 (0.62,0.73)		
Early decelerations		0.38 (0.33,0.44)	0.05 (0.06,0.28)	0.09 (0.01,0.17)
No	270	0.44 (0.36,0.51)		
Intermittent	189	0.26 (0.17,0.35)		
Recurrent	141	0.44 (0.34,0.55)		
Variable decelerations		0.56 (0.50,0.62)	0.16 (0.13,0.37)	0.41 (0.33,0.49)
No	35	0.17 (0.00,0.34)		
Intermittent	204	0.41 (0.32,0.49)		
Recurrent	361	0.69 (0.62,0.74)		
Late decelerations		0.77 (0.72,0.81)	0.06 (−0.02,0.16)	0.74 (0.67,0.80)
No	520	0.87 (0.84,0.90)		
Intermittent	62	0.13 (0.00,0.26)		
Recurrent	18	0.00 (0.00,0.00)		
Prolonged decelerations		0.75 (0.70,0.80)	0.48 (0.37,0.57)	0.53 (0.44,0.63)
No	372	0.80 (0.75,0.84)		
Yes	228	0.68 (0.60,0.74)		
Sinusoidal pattern		0.99 (0.99,1.00)	0.00 (−0.01,0.00)	0.99 (0.98,1.00)
No	598	1.00 (0.99,1.00)		
Yes	2	0.00 (0.00,0.00)		
Neonatal acidemia		0.55 (0.50,0.61)	0.18 (0.10,0.26)	0.14 (0.02,0.26)
No	358	0.63 (0.56,0.68)		
Yes	242	0.45 (0.37,0.53)		
pH<7.1		0.91 (0.87,0.93)	−0.02 (−0.05,−0.01)	0.90 (0.86,0.94)
No	572	0.95 (0.93,0.97)		
Yes	28	0.00 (0.00,0.00)		

CI: Confidence interval; FHR: Fetal heart rate; Pa: Proportions of agreement.

So, it is certain that fetal monitoring, as CTG, allows to evaluate FHR baseline variations, being them evidently related to fetal acid-base status *(Balayla et al., 2020)*, but it cannot predict values of neonatal pH. Moreover, the increased intervention of caesarean, as well as the limited specificity associated with the interpretation of the tracings, has raised the so called "Obstetrical Paradox" *(Balayla et al., 2019)*. To determine the predicting capabilities of fetal monitoring tracings *(Balayla et al., 2020)*, the Bayer's theorem can be applied, describing the probability of an event occurring based on prior knowledge of conditions that might be related to that specific event. In our case, event A is the abnormal fetal pH and event B is the abnormal tracing, where the theorem states that the probability of the event A, being the event B present, is equal to the probability of B given A as true, multiplied by the ratio between the independent

probability of A and the independent probability of B.

$$P(A|B) = P(B|A) \times P(A)/P(B) \quad (1)$$

This adds a statistical component to the approach of the clinician, considering not just the specific clinical context, in terms of parameters and features of the tracings, but also defining the risk and the probability of an event to take place, by how common that event occurs in the population.

Fetal wellbeing analysis using automatic methods

Using automatic methods is a way to improve and make clinicians' job easier, interpreting in a computerized manner the FHR tracing and identifying the typical features of it. Several research were and still are conducted in this field, with the purpose of recognizing automatically eventual occurrence of concerning event among the signals, making the analysis more objective and universally accepted and solving the problems related to the subjectivity of the medical personnel's opinion. This means finding a way to read, process, and classify the tracings that are acquired before and during labour, having a detailed and precise evaluation of FHRV, accelerations, decelerations, sinusoidal patterns, that is to say all those parameters that could be needed to evaluate the fetal wellbeing state.

Approaches developed in the last years are following different paths and focusing on various aspects that could be interesting, within the FHR tracing analysis. On the other hand, this variety of ways should converge in the same goal, which is preventing and properly treat fetal suffering, to achieve the biggest possible number of positive outcomes.

Investigating an optimal signal epoch length for cardiotocographic classification

The majority of studies on fetal monitoring and wellbeing analysis are based on CTG acquisition and lean on CTG classification. That is why defining a common method of treating the signal is fundamental even before the pattern identification itself.

Regarding this concern, a study conducted by Fuentealba et al. *(Fuentealba et al., 2020)* aimed to find the optimal length for signal epochs, in order to easier extract data of CTG signals from acquisitions of different duration. After cleaning the signal from artifacts, removing inconsistent FHR signal values (outside the range between 50bpm and 210bpm), and interpolating loss-of-signal data≤75s, the tracing is filtered with a window length of 15s.

Secondly, decelerations are identified, since they are treated as one of the most significant, although challenging, CTG signal patterns to assess the fetal condition. Then, the pre-processed FHR signal is detrended by the subtraction operation between the pre-processed FHR signal and the floating line.

Features extraction is performed to derive indicators, to which statistical indexes are correlated, in order to evaluate the reliability of the experiment. The procedure is in fact repeated for a certain number of time epochs, with the overmentioned purpose to identify the ideal time interval. These epochs consist of FHR data of 20 , 25, 30, 35, 40, 45, 50, 55, and 60 minutes long, sliding in steps of 5 minutes.

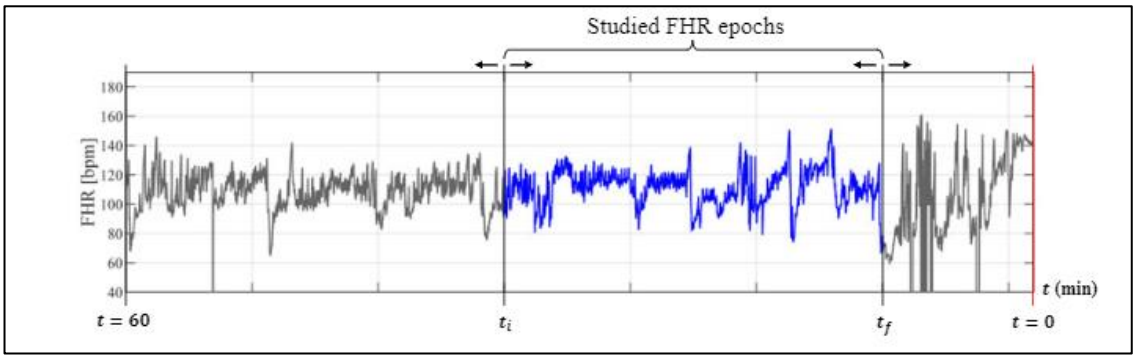

Figure 17. Representation of studied FHR epochs of variable length and location[8]

Results show that the classification performance depends considerably on the selected epoch, and, in a particular way, it results to have the worst result for a segment between 60 and 30 minutes, while the best performance is achieved by considering an epoch of 30 minutes long before the delivery. This leads to the consideration of a 30-minutes window as an optimal length for automatic FHR analysis during labour.

Analysis of decelerations to prevent hypotension and acidaemia

A particular interest is given to the study of decelerations, which are significant parameters to correlate with fetal hypoxia and acidaemia. To reach the purpose to obtain a computerized analysis of this feature, signals from electronic fetal monitoring (CTG) are acquired and sent to the computer as raw signal, which will be sampled, stored and processed *(Boudet et al, 2020)*. Once defined that the deceleration is a period during which the FHR is below the baseline for at least 15s and reaches a value of at least 15 bpm over the baseline at any moment during that

[8] FHR epochs are defined by an initial (t_i) and a final (t_f) time. In this figure, t= 0 corresponds to the delivery time, and the time t= 60 means one hour before delivery

period, it is necessary to determine an algorithm for an automated analysis.

In 2020, Boudet et al. developed a Matlab Toolbox with this aim, containing twelve morphological analysis methods (AAM), with specific baseline algorithms. These methods are then compared, to evaluate the best performance among them, grading as more satisfying the method of Lu et al. Starting from that, the toolbox will also be able to reproduce an experiment on the same dataset, visualize and better understand problematic patterns and develop and test new AAMs. The aim of using a toolbox of this kind, is therefore to analyse FHR signals, quantify pathological features and finally predict the risk of acidosis, providing support to the clinicians and improve the objectivity of risk evaluation.

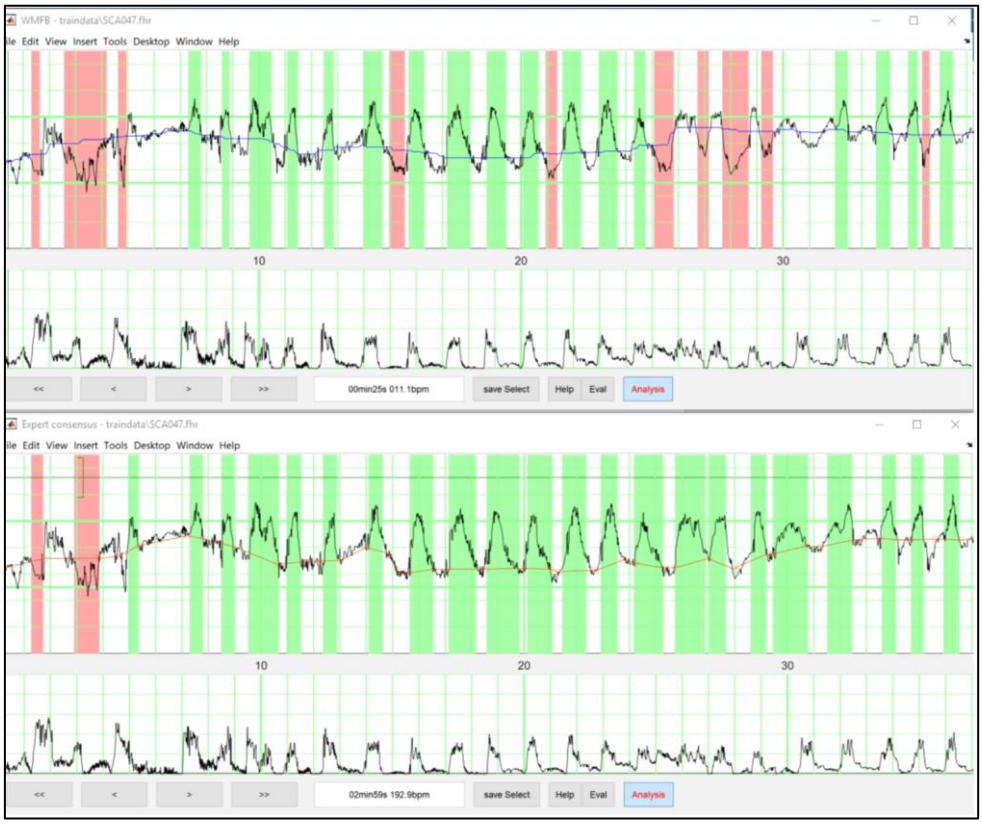

Figure 18. Matlab toolbox VS expert consensus for acceleration (green) and deceleration (pink) identification (adapted from Boudet et al., 2020)

According to other research, once decelerations are detected, they are not just taken *per se*, but it would be more useful to consider their area (DA) or their capacity (DC). Respectively, DA is strongly associated with fetal acidaemia, but its calculation is related to accuracy of baseline FHR, while DC does not rely on correct identification of FHR baseline and decelerations, and it is very tolerant in terms of noise or loss of contact during recording *(Georgieva et al., 2021)*. Within a set period of time, a number of decelerations is determined, considering duration (in

seconds) and depth (in bpm) for each one. Deceleration area could then be measured by drawing the contours of each deceleration, forming a sort of triangular shape, or, more precisely, according to the actual characteristics of the tracings, as in *Figure 19 (Gyllencreutz et al., 2021)*. Choosing to use the area under the curve method (AUC), instead of the formula *deceleration width*depth/2,* is indeed a more accurate approach, which allows obtaining satisfying results in terms of correlations with clinical intrapartum parameters, as lactate concentration at fetal scalp blood sampling (FBS), indicating deceleration area as a promising index for predicting fetal acidaemia *(Gyllencreutz et al., 2021)*.

For what concerns deceleration capacity (DC), its measurement is related to HRV and more accurately, it consists of averaging the magnitude of all falls in FHR between successive heartbeats, to provide an integrated measure of the magnitude and frequency of FHR decelerations *(Georgieva et al., 2021)*. DC reduces some practical constraints in the calculation, being a possible substitute to DA in predicting fetal acidaemia, as well a potential parameter to consider for a computerized identification method.

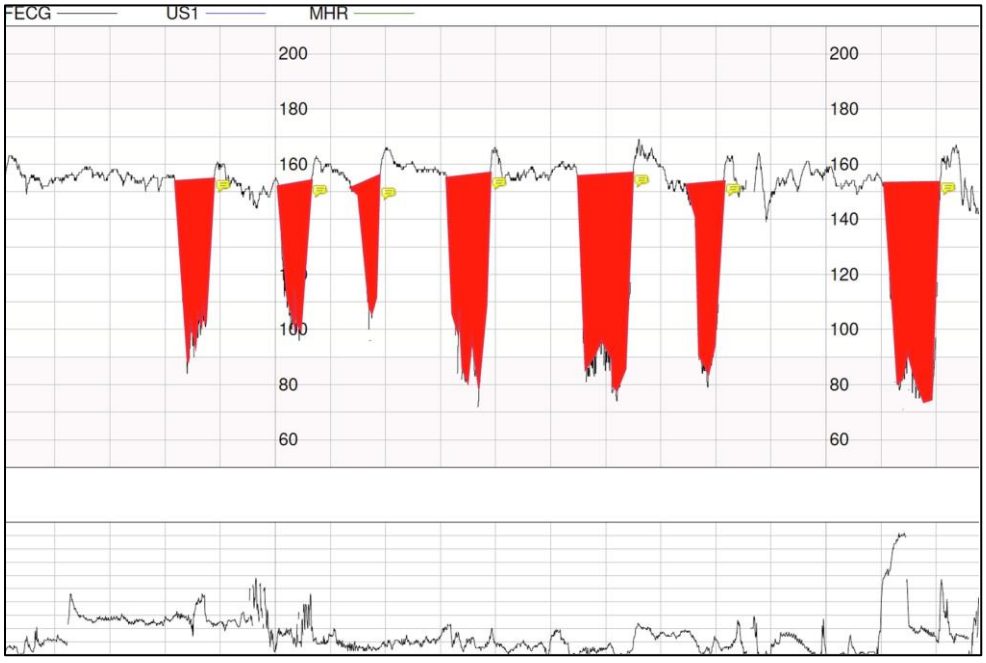

Figure 19. Accurate calculation of deceleration features (Gyllencreutz et al., 2021)

A further relevant parameter that can be extracted by reading a CTG tracing is the distance to healthy state. According to Roux et al. *(Roux et al., 2021)*, this Distance (D_k) is intended to be a value that expresses a relation between FHR and biological parameters, to represent how the actual state differs from the physiological one. To derive the value of D_k, a series of calculations

is accomplished, deriving former parameters that are then summed up in a final equation, to obtain the expression of the distance itself.

In this specific research, Roux et al. chose to derive FHR tracings from animal model, in particular a pregnant sheep model, considering four parameters. These four quantities are computed from the whole FHR signal to probe its dynamics along the complete experiment, and they are: the average variation of the FHR over the prescribed time scale; the FHR variability over the time scale as the standard deviation; the ratio of the first two; a quantity very similar to Approximate Entropy[9] or Sample Entropy[10], that provides a measure of the information content of the FHR signal at the given time scale. The FHR-derived parameters are correlated to metabolites data (pH, lactate and BE), obtained by blood sampling performed at specific times during the experiment. Among them, pH is regarded as very important in acidosis diagnosis and can be an index of hypoxia-ischemia, due to reduced cerebral blood flow, as a consequence of cardiovascular decompensation (CVD).

Table 5. Correlation coefficients between the four individual features, their vectorial combinations, and the three measurements pH, BE, and Lactate. (Roux et al. 2021)

	m_{LT}	σ_{LT}	R_{LT}	h_{LT}	$\|\|\bar{u}\|\|$	D	pH	BE	Lactate
m_{LT}	1.00	–0.51	0.77	0.60	0.29	–0.87	0.53	0.48	–0.36
σ_{LT}	–0.51	1.00	–0.19	–0.43	–0.35	0.61	–0.42	–0.36	0.35
R_{LT}	0.77	–0.19	1.00	0.42	0.14	–0.63	0.50	0.48	–0.35
h_{LT}	0.60	–0.43	0.42	1.00	0.89	-0.76	0.50	0.43	–0.32
norm $\|\|\bar{u}\|\|$	0.29	–0.35	0.14	0.89	1.00	–0.50	0.35	0.29	–0.21
distance D	–0.87	0.61	–0.63	–0.76	–0.50	1.00	–0.61	–0.53	0.44
pH	0.53	–0.42	0.50	0.50	0.35	–0.61	1.00	0.95	–0.77
BE	0.48	–0.36	0.48	0.43	0.29	–0.53	0.95	1.00	–0.72
Lactate	–0.36	0.35	–0.35	–0.33	–0.21	0.44	–0.77	–0.72	1.00

Data from all 14 animals and all available time-windows were used. Colored values indicate the quantity which correlates better with the biochemical measurement; it is always the distance D.

[9] Approximate entropy (ApEn), has been recently introduced as a quantification of regularity in time-series data, quantifying regularity and complexity, which can be applied to a wide variety of relatively short and noisy time-series data, as heart rate acquisition signals could be *(Pincus, 1995)*

[10] Sample entropy (SampEn) is based on the same principle of ApEn, but allows to reduce the bias of the Approximate entropy, being more consistent with theory for dataset with known probabilistic content *(Lake et al., 2002)*

Table 5 states the existing correlation between the FHR features and the metabolic parameters. For the belief that each of the four parameters provides a piece of information to understand a specific FHR signal, they are grouped in a unique vector, that refers to a specific animal in a specific interval of time *k,* measured in the long-term LT. Each parameter is considered in its normalized form, by the relative standard deviation, over the total available time interval of size T.

$$\vec{u}_k = \left(\frac{m_k^{\mathrm{LT}}}{m_{\mathrm{RMS}}^{\mathrm{LT}}}, \frac{\sigma_k^{\mathrm{LT}}}{\sigma_{\mathrm{RMS}}^{\mathrm{LT}}}, \frac{R_k^{\mathrm{LT}}}{R_{\mathrm{RMS}}^{\mathrm{LT}}}, \frac{h_k^{\mathrm{LT}}}{h_{\mathrm{RMS}}^{\mathrm{LT}}} \right) \qquad (2)$$

Finally, the distance is defined as the module of the vector $\vec{u}_k$ which describes the state in the k[th] time-window and $\vec{u}_0$, which describes the state in the first time-window [0; T]:

$$||Dk = \vec{u}_k - \vec{u}_0|| \qquad (3)$$

It is observed that this distance varies in concomitance with metabolic parameters, more precisely with the values of pH, making visible that using all four FHR features simultaneously, by considering the vector $\vec{u}_k$, aggregates the correlations among all the parameters. This also relates higher values of Dk with the onset of CVD (the red vertical line in *Figure 20* indicates the CVD time), making this parameter a valuable alert for the fetal health state.

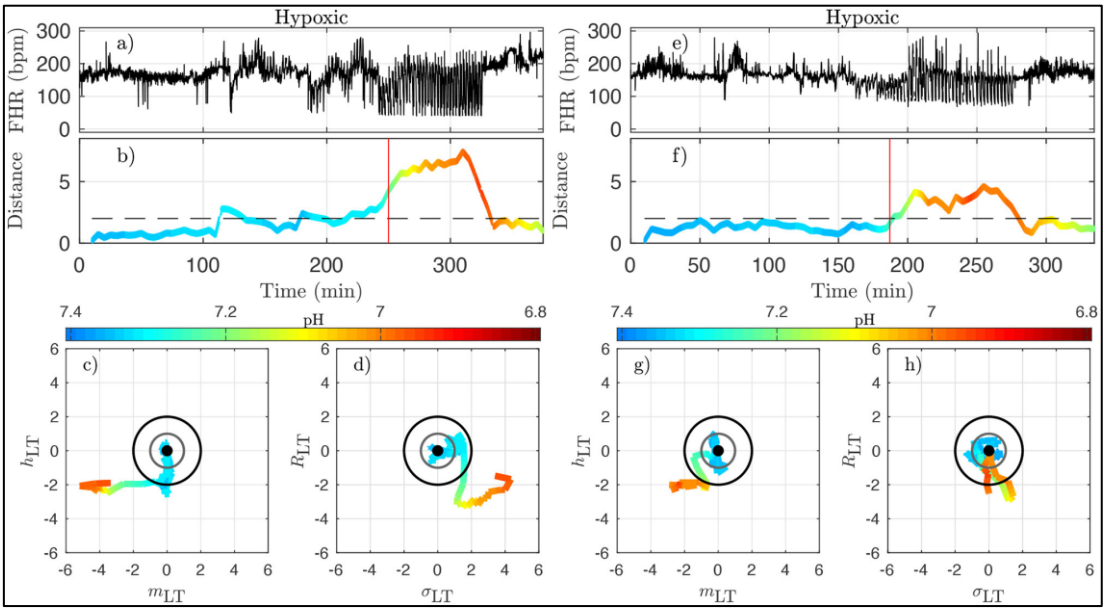

Figure 20. Two examples of hypoxic animals (Roux et al. 2021)

A former study for fetal well-being evaluation

A previous approach *(Brizzola, 2020)*, to evaluate the fetal well-being state during labour, consisted of calculating deceleration area, amplitude, and duration from the fetal heart rate signal, acquired through cardiotocographic data acquisition. The FHR signals were taken from a database of CTG acquisitions on pregnant women (*CTU-CHB Intrapartum Cardiotocography Database*) and decelerations were identified among 552 FHR plots. The area was derived as a quadrangular shape, being the horizontal side given by the deceleration duration and the vertical side given by the amplitude in terms of maximum and minimum values of FHR. For each subject, pieces of information about neonatal post-partum parameters were collected. Areas, amplitudes, and durations of each valid deceleration were subsequently correlated to neonatal post-partum parameters, such as Apgar, Base Excess (BE), and pH, which are currently the most reliable parameters to evaluate the health condition of a new-born. Correlation coefficient *R* and *p-value* were extracted for each couple of deceleration-postpartum parameter and between the postpartum neonatal parameters themselves. An expected value of R as much as possible near to 1 or -1, as well as a *p-value* <0.05, would have been synonyms of a strong correlation among the overmentioned parameters. The actual values obtained in this analysis are reported in *Table 6-7*.

Table 6. Correlation values. Postpartum neonatal parameters

Correlation	R	p
Apgar/pH	**0.46**	**$<10^{-21}$**
BE/Apgar	**0.38**	**$<10^{-14}$**
pH/BE	**0.83**	**$<10^{-100}$**

Table 7. Correlation values. Deceleration-Postpartum neonatal parameters

	pH		Apgar		BE	
	R	p	R	p	R	p
Average area	**-0.22**	**$< 10^{-4}$**	**-0.13**	**$< 10^{-2}$**	**-0.26**	**$< 10^{-6}$**
Average amplitude	**-0.01**	**0.74**	**-0.013**	**0.79**	**-0.05**	**0.30**
Average duration	**-0.24**	**$< 10^{-6}$**	**-0.18**	**$< 10^{-3}$**	**-0.25**	**$< 10^{-6}$**

Unfortunately, this correlation has revealed an absence of proportionality between each of the deceleration parameters and the neonatal post-partum parameters, making it improbable to use this approach to determine acidosis or insufficient oxygenation.

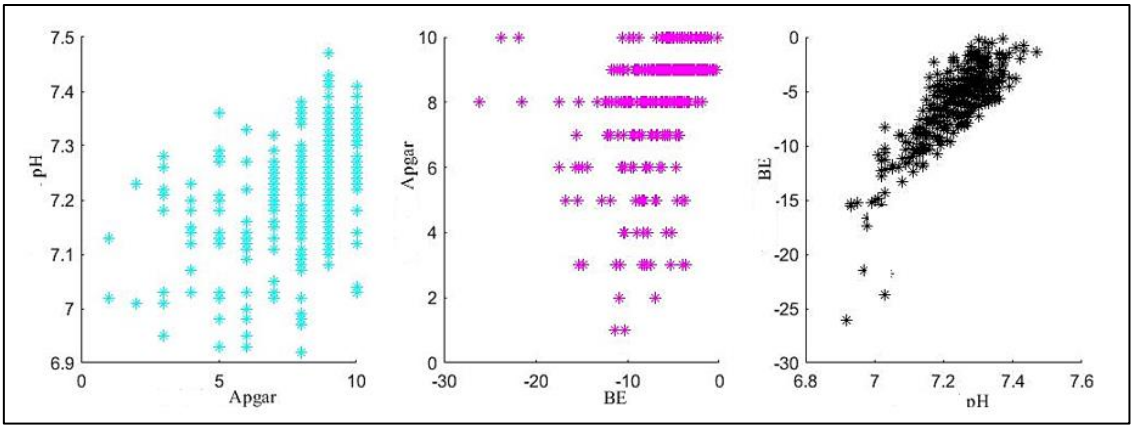

Figure 21. Correlations between neonatal post-partum parameters.

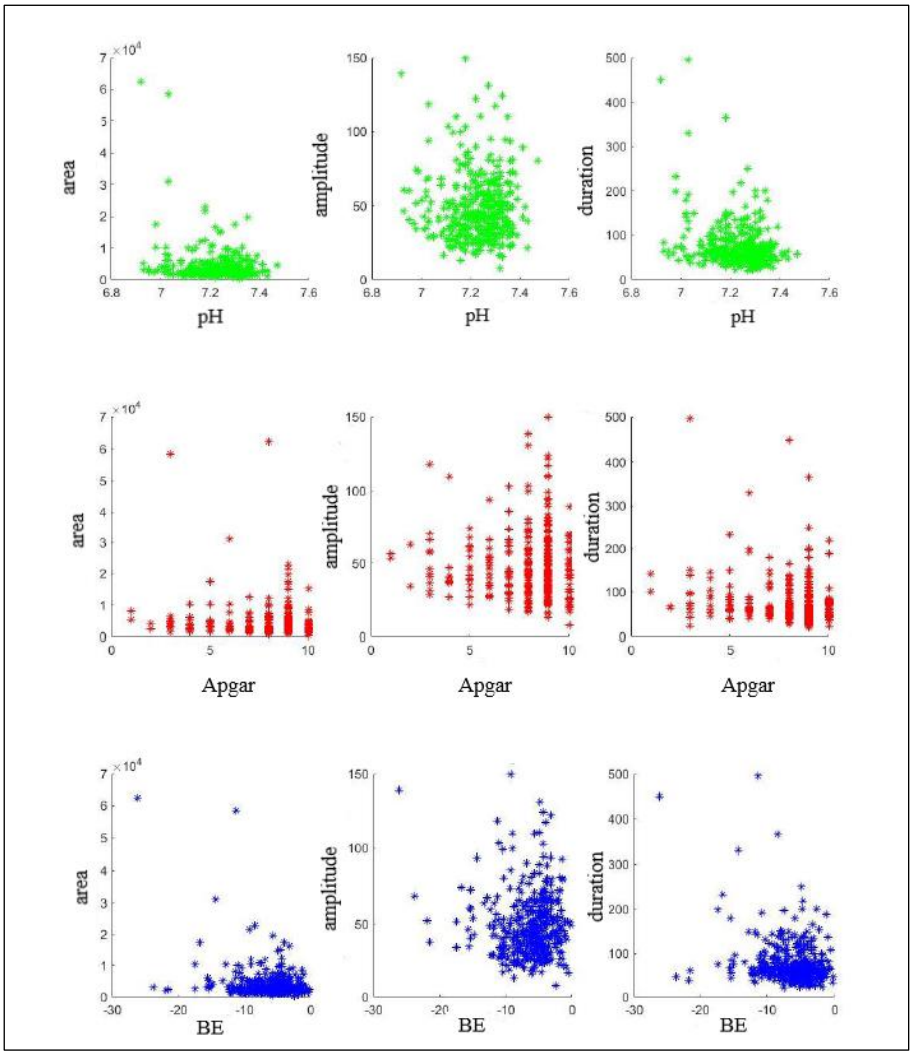

Figure 22. Correlations between decelerations and post-partum neonatal parameters

Despite these results, the research is still open to find new methodologies to identify workable solutions to read FHR signals from CTG as a predictor of fetal suffering.

Interpretation of Average Acceleration and Deceleration Capacity computed through Phase-Rectified Signal Averaging

Average deceleration capacity *(Rivolta et al., 2020)*, and its equivalent for accelerations (Average acceleration capacity), are recognized and accepted by the bioengineering scientifical community as suitable indexes for CTG tracks evaluation. Therefore, they could be introduced in a possible method for the accomplishment of automatic analysis. Particularly, recent studies supported the idea of using acceleration (AC) and deceleration capacity (DC) as parameters to be interpreted to analyse the functioning of the autonomic regulation and with it of the eventual occurrence of anomalies and alert conditions.

Initially focusing on DC, it can be computed using Phase-Rectified Signal Averaging (PRSA) *(Bauer et al., 2006)*, an algorithm that show high sensitivity to discriminate among various clinical and preclinical conditions using FHR traces, such as fetal distress, cardiovascular risk, and intrauterine growth restriction *(López-Justo et al., 2021)*. Therefore, this technique *(Bauer et al., 2006)* is considered to provide an estimate of the autonomic regulation of the fetal heart rate, even in case of anomalies in the tracing, as de-synchronizations, miss-detected beats and signal losses. PRSA use follows the approach introduced in the HR signal analysis by Bauer et al. in their research about mortality after myocardial infarction, so on adult subjects, where decelerations in heart rate were also seen as prognostic markers, as it is for the fetal heart rate. Therefore, the signal acquired in Bauer et al. research is not a CTG, but instead a 24h Holter data acquisition on elderly patients, who all had infarction.

The signal was treated applying PRSA to process sequences of RR intervals[11] on the Holter recordings, allowing to derive accelerations, decelerations and their modulations, quantified by AC and DC. PRSA also permits to extract periodicities from the signals, so that no-stationary patterns can be excluded from the analysis, since they can be generated by noise or artifacts and can affect the quality of the evaluation. It also synchronises the phases of all components, even if they have different frequencies or time scales, making possible to integrate all the contributions, which brings to deceleration capacity computation.

More in detail, as represented graphically in *Figure 23*, quantification of DC in Bauer et al. consists of 5 steps, being step 1 the definition of anchor point, step 2 the definition of segments,

[11] The RR interval is the time between two successive R waves of the QRS signal on the electrocardiogram and it is a function of intrinsic properties of the sinus node as well as autonomic influences *(Lanfranchi et al., 2017)*

step 3 the phase rectification, step 4 the signal averaging and step 5 the actual quantification of DC (as well as AC).

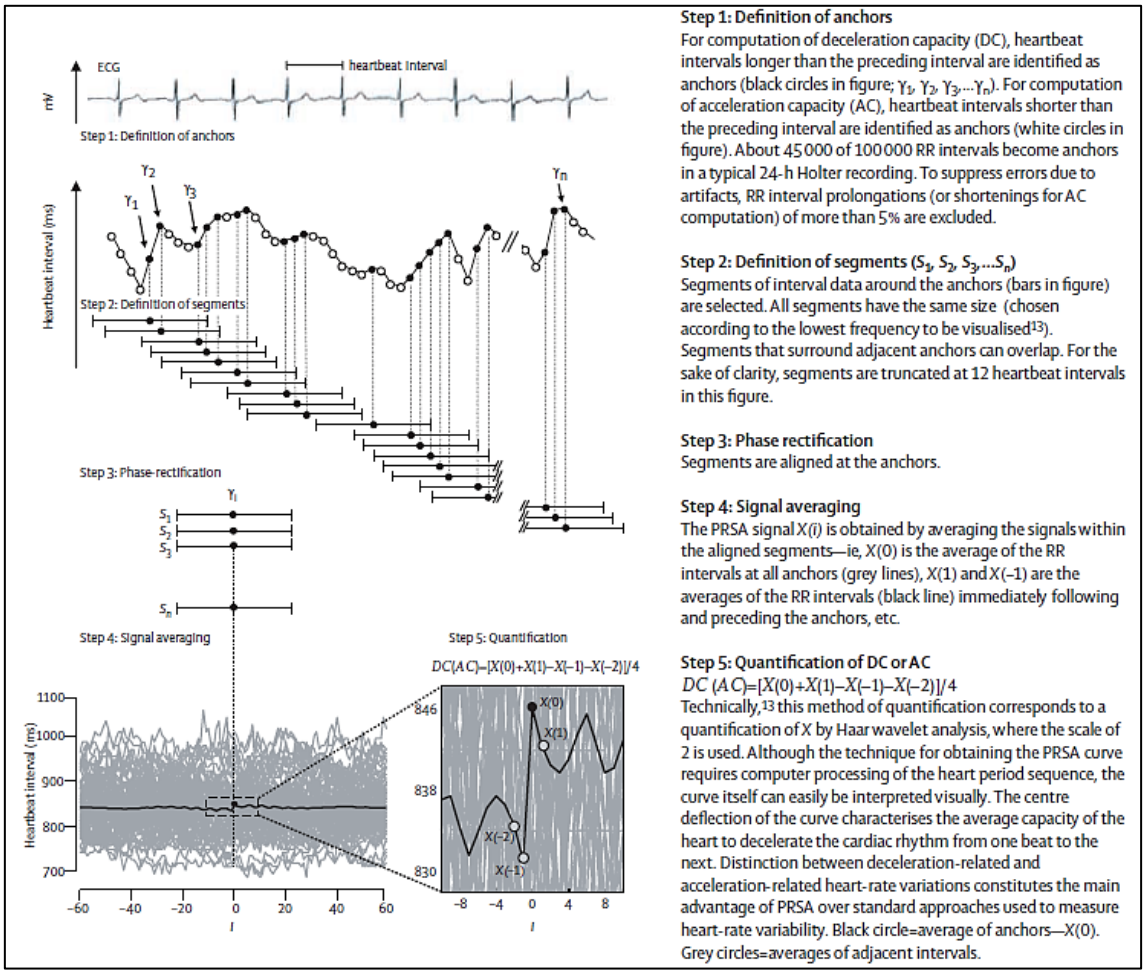

Figure 23. Assessment of deceleration capacity by PRSA in a 24-h recording of heartbeat intervals (Bauer et al., 2006)

This PSRA technique was applied by Rivolta et al. *(Rivolta et al., 2020),* adapting the approach for adult heart rate to a research more focused on fetal heart rate, with the aim to clarify some behaviours of acceleration and deceleration capacities. DC is computed starting from RR series and considering each time point *t* as an *anchor point.* Being *T* an integer that sets the timescale, the deceleration list A_{DC} is calculated as

$$A_{\mathrm{DC}} = \left\{ t : \frac{1}{T}\sum_{i=0}^{T-1} \mathrm{RR}[t+i] > \frac{1}{T}\sum_{i=1}^{T} \mathrm{RR}[t-i] \right\} \quad (4)$$

The anchor is the central point of a window of 2L length, being it in position L+1, so that there are as many windows as the number of anchor points. The PRSA series are obtained by aligning and averaging the total amount of windows, then they need to be introduced in the formula for DC calculation, considering a scale named *s*.

$$\mathrm{DC} = \frac{1}{2s}\sum_{i=1}^{s}\mathrm{PRSA}[L+i] - \frac{1}{2s}\sum_{i=0}^{s-1}\mathrm{PRSA}[L-i] \quad (5)$$

For the calculation of AC, the "accelerations' list" A_{AC} is instead built by changing the direction of the inequality in (4) and from it the PRSA is computed and put in the same equation as (5). T, L and *s* affect the calculation of PRSA series; thus their values need to be properly set before the computing procedure. Specially, *(Sassi et al., 2014*). the value of *s* refers to the frequency band of the oscillations, while T participates in the choose of the anchor point and L should be larger than the length of the period of the slowest oscillation of interest.

In order to evaluate DC *(Rivolta et al., 2020)* through a stochastic process, the overmentioned equations can be used to compute the estimated PRSA, that will be associated to the theoretical value of the PRSA, which is instead correlated to the properties of the stochastic method itself. For this purpose, Rivolta et al. used a stationary Gaussian stochastic process *X* with mean μ_X= 0 and autocorrelation function $\rho_X(k)$. Considering 2L as the number of consecutive samples, the vector x is defined as the transpose of the samples from 1 to 2L, as follows.

$$x = [x_1, x_2, \ldots, x_{2L}]^T$$

From the first 2L values of $\rho_X(k)$, the covariance matrix Σx is built and introduced in the formula to derive the probability density function (pdf).

$$\mathrm{pdf}_X(\mathbf{x}) = \frac{(\det \boldsymbol{\Sigma}_\mathbf{x})^{-\frac{1}{2}}}{(2\pi)^L} e^{-\frac{1}{2}\mathbf{x}^\intercal \boldsymbol{\Sigma}_\mathbf{x}^{-1}\mathbf{x}}$$

The anchor point (AP) is located, as previously, in position x_{L+1}, while the deceleration list is derived as

$$\mathcal{A}_{\mathrm{DC}} = \{\mathbf{x} : \mathbf{g}^{\intercal}\mathbf{x} > 0\}$$
$$\mathbf{g} = [0, \cdots, 0, \underbrace{-1, \cdots, -1}_{T \text{ values}}, \overbrace{1}^{\text{AP}}, \underbrace{\cdots, 1}_{T \text{ values}}, 0, \cdots, 0]^{\intercal}. \quad (6)$$

Two hyperspaces are defined by g and within them it is possible to determine the expected value of x, which would correspond to the relative PRSA series, computed for each sample *i*

$$\mathrm{PRSA}[i] = \mathrm{E}[x_i]|_{\mathbf{x}\in\mathcal{A}_{\mathrm{DC}}} = 2\int_{\mathbf{g}^{\intercal}\mathbf{x}>0} \mathbf{e}_i^{\intercal}\mathbf{x}\mathrm{pdf}_X(\mathbf{x})d\mathbf{x}, \quad (7)$$

In order to solve the integral in (7), after two changes of variables, the PRSA is expressed as

$$\begin{aligned}\mathrm{PRSA} &= \left(\sqrt{\frac{2}{\pi}}\mathbf{e}_{L+1}^{\intercal}\mathbf{H}\mathbf{D}^{\frac{1}{2}}\mathbf{U}^{\intercal}\mathbf{I}\right)^{\intercal} \\ &= \sqrt{\frac{2}{\pi}}\mathbf{U}\mathbf{D}^{\frac{1}{2}}\mathbf{H}^{\intercal}\mathbf{e}_{L+1} = \mathbf{p}.\end{aligned} \quad (8)$$

Finally, the deceleration capacity is evaluated after a wavelet transform, using a Haar mother wavelet function, at scale s (the third free parameter) and location L+1.

$$DC = \frac{1}{2s}\mathrm{h}^{\mathrm{T}}\mathrm{p} \quad (9)$$

$$\mathrm{h} = [0, \ldots, 0, \underbrace{-1, \ldots, -1, 1}_{s \text{ values}}, \underbrace{\ldots, 1, 0}_{s \text{ values}}, \ldots, 0]^{\mathrm{T}}$$

Also in this case, the derivation of AC theoretical values is quite similar to the one related to DC, with the exception of (6), which is

$$\mathrm{A_{AC}} = \{x : -\mathrm{g}^{\mathrm{T}}\mathrm{x} > 0\} \quad (10)$$

making AC a negative minus signed expression.

$$\mathrm{AC} = -\frac{1}{2s}\mathrm{h}^{\mathrm{T}}\mathrm{p} \quad (11)$$

Further studies investigated on the use of different wavelet for the PRSA transformation applied in DC estimation *(Rivolta et al., 2021)*. Among 5 wavelets, including Shannon, Morlet and two versions of Poisson's, besides Haar, a ranking was performed, for finding the more appropriate wavelet for acidaemia detection. They should all enhance decelerating trend and be sensitive to slow changes in FHR, but they present some divergences. Haar and Poisson families function as derivative filters, enhancing the trend as expected, while Morlet and Shannon are equivalent to band pass filters, more sensitive to low frequency components.

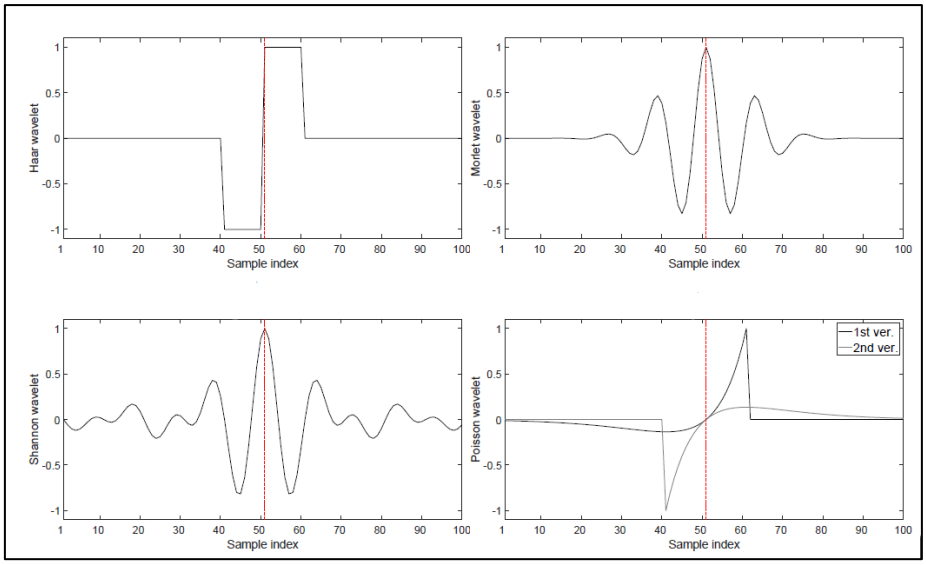

Figure 24. Example of five wavelets (Rivolta et al. 2021)

According to this study, the results suggest that different wavelets may be more appropriate for acidaemia detection than Haar wavelet, since it was outperformed by Shannon and Poisson wavelets. In fact, the second version of Poisson wavelet appeared in the ranking four times (the highest), while the Morlet's did not appear in the top five.

Once PRSA series are derived *(Rivolta et al., 2020)*, both in their theoretical and estimated values, it is possible to make a comparison between the two of them. This provides and evident matching, which increases with a higher number of samples involved in the analysis.

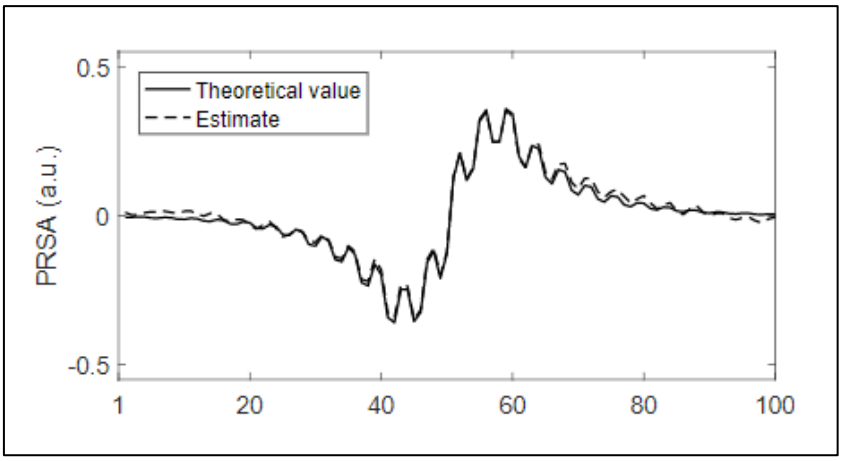

Figure 25. Theoretical and estimated values of PRSA (adapted from Rivolta et al. 2020)

Considering that differences between AC and DC generate asymmetric increasing or decreasing trends in the signal, and that capacities can differ from each other in case of non-stationarities or non-gaussianities, Rivolta et al. considered relevant the introduction of another index, which is obtained by a combination of the previous two: the Deceleration Reserve (DR).

$$DR=DC+AC \qquad (12)$$

DR is assumed to be correlated to fetal distress and it is compared to AC and DC in terms of discrimination power, to identify acidotic foetuses among healthy FHR signals.

Two kinds of approaches were followed: first with data from pregnant sheep model of labour and then on CTU-UHB Intrapartum Cardiotocography Database from Physionet.

While in times far from labour the signal results to be quite stationary, with almost identical AC and DC values that make DR near to zero, during labour, when the signal is non- stationary, the DR outcome is expected to be different from zero. This is confirmed by the observations on animal model, where DR has a significant value in correspondence of severe decelerations episodes, besides showing a statistically significant correlation with biomarkers.

DR is proved to be a discriminant parameter for acidosis and foetal hypoxia in CTU-UHB data analysis, too, even if with some limitations due for example to the reduced number of acidotic foetuses in the database or to some corrections applied to the signal itself. Despite that, this methodology is assumed as a good fit to avoid false positives, both for animal and human data.

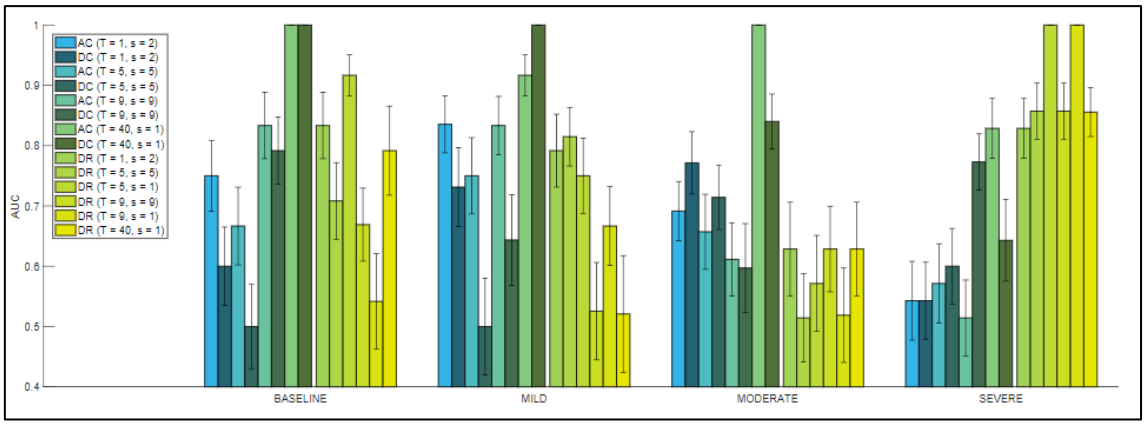

Figure 26. Average and standard deviation of AUC values in discriminating normoxic and hypoxic sheep foetuses after power correction (Rivolta et al., 2020)

In addition, these differences between AC and DC, expressed in the form of DR, can be related to the immaturity of the fetal cardiac autonomic nervous system, which can be identified observing the response to intense uterine activity during labour *(López-Justo et al., 2021)*.

While none of the mean values of A_{AC} or A_{DC} indices show significant differences between the Term and Preterm groups of signals, DR in Lopez-Justo et al. exhibits, as expected, relevant differences between Term and Preterm. This is closely related to asymmetry in the FHR, which is a characteristic of non-equilibrium states and, specifically in foetuses, it changes along foetal development, depending on the sympathetic activity progressing toward delivery. Asymmetric behaviour of the RR series in fetal heart rate differs between Term and Preterm labour, and it can be studied by quantifying this asymmetry through various indices.

Porta's index ($PI\%$) is computed as:

$$PI\% = \frac{N(\Delta RR^{-})}{N\Delta RR \neq 0} \cdot 100 \qquad (13)$$

The negative ΔRR^{-} refers to accelerations, while the positive ΔRR corresponds to the decelerations. So, $PI\%$ is higher that 50 if the number of accelerations is superior to the number of decelerations.

The Guzik index ($GI\%$) calculates the deceleration and acceleration influence into short-term HR data, considering the sum of the square of positive ΔRR^{+} to the cumulative sum of square of ΔRR.

$$GI\% = \frac{\sum_{i=1}^{N(\Delta RR^{+})} \Delta RR^{+}(i)^2}{\sum_{i=1}^{N(\Delta RR\ )} \Delta RR\ \ (i)^2} \cdot 100 \qquad (14)$$

Ehlers' index defines the distribution of ΔRR , indicating that the series is asymmetric if EI is far from 0. *EI*> 0 if the signal is distributed toward positive values, that means that the average magnitude of $|\Delta RR^{+}|$ is larger than that of $|\Delta RR^{-}|$

$$EI = \frac{\sum_{i=1}^{N(\Delta RR\ )} \Delta RR\ \ (i)^3}{\left(\sum_{i=1}^{N(\Delta RR\ )} \Delta RR\ \ (i)^2\right)^{\frac{3}{2}}} \qquad (15)$$

Results states that *PI%* does not underline a particular difference between Term and Preterm group, while this happens for *GI%* and *EI.* These indexes increase in Term group, compared to the Preterm, showing a higher number of decelerations in Term labour, with an increased parasympathetic nervous activity (expressed by increased *GI%).*

This supports the idea that acceleration and deceleration analysis, using PRSA to determine various indexes correlated to them, can allow to highlight and quantify correlations with the response of the foetus to stress during labour, as well as other factors that could eventually result into a risk for the foetal wellbeing.

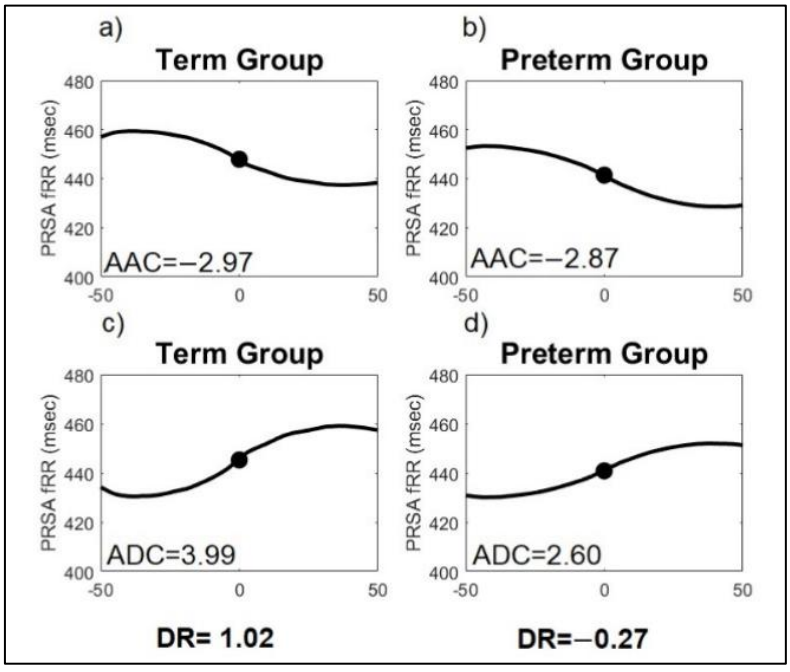

Figure 27. Examples of Phase-Rectified Signal Averaging (PRSA), comparing Term and Preterm Group (López-Justo et al., 2021)

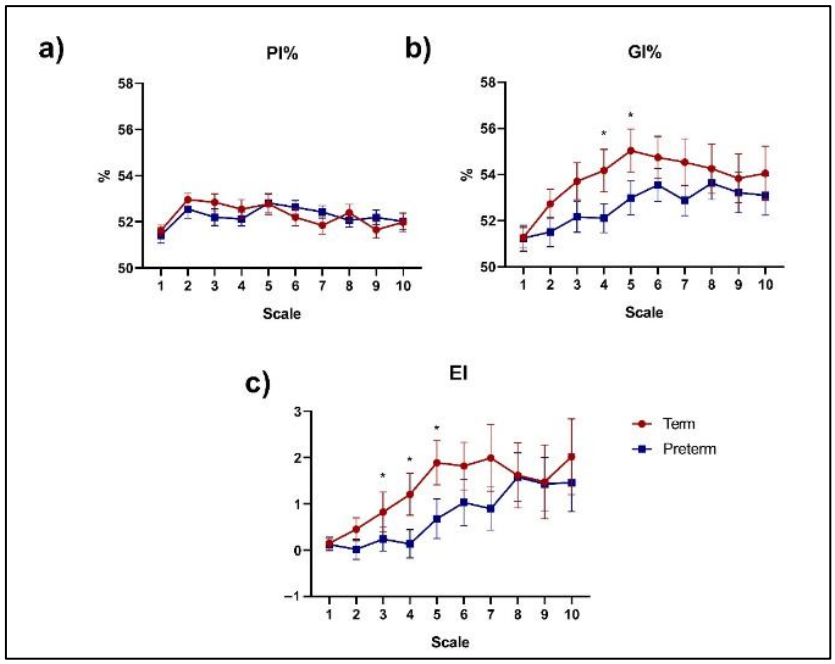

Figure 28. Asymmetry indices of fetal beat-to-beat R-R intervals time series (López-Justo et al., 2021)

Chapter 4

Towards phase-rectified signal averaging technique for foetal heart rate signal processing

CTU-CHB Intrapartum cardiotocography database

The CTU-CHB database was acquired by the Czech Technical University (CTU) in Prague and the University Hospital in Brno (UHB) at the UHB itself, between 2010 and 2012. It contains 552 CTG recordings, which were selected among a total of 9164 recordings.

Each CTG recording has a duration of at most 90 minutes, starting to record no more than 90 minutes before the actual childbirth. It reports both fetal heart rate (FHR) and uterine contractions (UC), which are then sampled at 4Hz and made as homogeneous as possible, by following certain criteria, as:

- Singleton pregnancy
- Gestational age >36 weeks
- No a priori known developmental defects
- Duration of stage 2 of labour ≤ 30 minutes
- FHR signal quality (i.e. percentage of the recording during which FHR data were available) > 50% in each 30-minute window
- Available analysis of biochemical parameters of umbilical arterial blood sample (i.e. pH)
- Majority of vaginal deliveries (only 46 caesarean section (CS) deliveries included)

Additional parameters were collected for all recordings:

- Maternal data: age; parity; gravidity.
- Delivery data: type of delivery (vaginal; operative vaginal; CS); duration of delivery; meconium-stained fluid; type of measurement (i.e. ultrasound or direct scalp electrode).
- Fetal data: sex; birth weight.
- Fetal outcome data: analysis of umbilical artery blood sample (i.e. pH; pCO2; pO2; base excess and computed BDecf); Apgar score; neonatology evaluation (i.e. need for O2; seizures; admission to NICU)
- Expert evaluation of the CTG data "Gold Standard" evaluation based on annotation of

the signals by 9 expert obstetricians (following FIGO guidelines used in the Czech Republic) including variability/confidence for each signal.

To perform our analysis *(Romagnoli et al., 2020)*, two folders, "signals" and "annotations", were used and loaded on Matlab, to process and analyse the contained data, which are respectively the 552 FHR recordings, named from "1001m.mat" to "2046m.mat", and the annotations for each of the overmentioned signals. These annotations present information about bradycardia, tachycardia, acceleration, deceleration and uterine contraction, identified according to their definitions provided by FIGO and indicated as BC, TC, ACC, DEC and UC. Another folder is also used for the purpose of this study, containing the neonatal post-partum parameters, in detail pH, Apgar and BE, which are acquired after the childbirth for each of the 552 subjects who are considered in the database. These data would provide significant information about the wellbeing state of the foetuses who underwent the recording and the outcome of the correspondent labour and delivery.

Methods

From the *CTU-CHB Intrapartum cardiotocography database,* 552 recordings, related to the same number of subjects, on whom data were acquired during labour, are used in this analysis. Uploading and correcting the signals are the initial steps of the procedure, performed by the compiling of a Matlab code (on *Matlab R2020a* version). The signals are sampled at 4Hz and have a gain of 100, therefore the amplitude values are divided by 100. So, each track is expressed as the behaviour of the fetal heart rate (in bpm) on a time interval (in minutes) that corresponds to the duration of the acquisition during labour, and for that reason there is not a standard period of time, but it varies from a subject to another. Data loss is corrected, applying a function that identifies the points of signal falling to zero and performs a linear interpolation. Despite that, some tracks still present a percentage of zeros higher than the 10%. To perform a further correction, without the elimination of an excessive amount of signals from our set, each recording is divided into three equal parts. Percentage of zeros, intended as the amount of zeros over the total number of values of the vectors, is calculated for the three sections. If it exceeds 10%, the related part is the only one to be ejected, and not the total signal, allowing to maintain that subject in the database, even with a shorter recording.

A folder containing annotations about each of the subjects is uploaded and from it, accelerations and decelerations onset and offset points are extracted. In this approach, we will not use the calculation of acceleration or deceleration interval itself, but it is necessary to verify the

presence of acceleration, deceleration, or both. If one of these conditions results as “true”, the DR deriving procedure will begin.

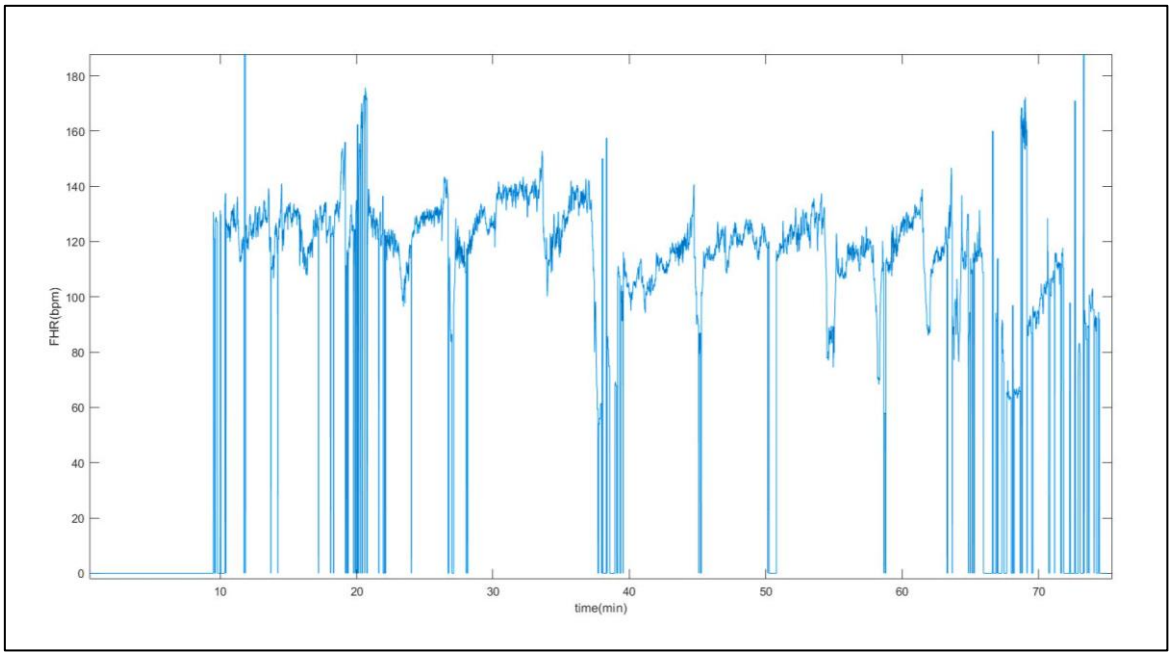

Figure 29. Original signal, before data loss interpolation

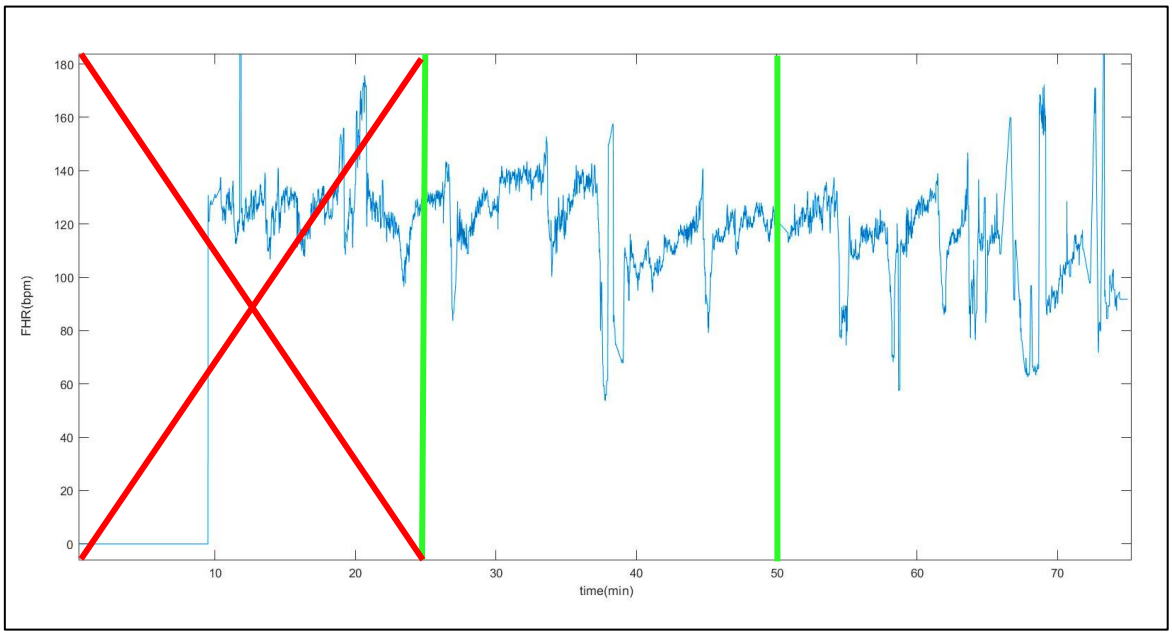

Figure 30. Interpolated signal divided into three equal parts. If the percentage of zeros is > 10%, the portion of the signal is deleted

In the first place, fetal RR is needed to be derived, since the amplitude of the signals is expressed

in bpm in our database. We need to go from beats per minute to seconds, since the cardiotocography expresses the frequency of the fetal heartbeats, while we would need time intervals to calculate RR intervals. RR is generally expressed in ms, therefore a further conversion from seconds to milliseconds is done. RR values equal to *Inf* are checked and eventually eliminated by the series.

Next, we can use the RR series as an input for two functions, *DC* and *AC,* which would give as output respectively the deceleration capacity and acceleration capacity, once verified by an *if* clause which checks that decelerations and accelerations are present, and that the corresponding RR series is not empty. In order to function, *DC* and *AC* also need three values to be set, in particular way L, T and s need to be defined. For this analysis, we set L = 40, T =1, and s =2, using values from previous research concerning the DR calculation *(Rivolta et al., 2020).*

More in detail, *DC* and *AC* calculate the acceleration and deceleration capacities deriving the acceleration or deceleration list, knowing the RR series and the value of T, being an integer that sets the timescale. From that, the PRSA series are derived, getting the anchor point values as the central point of a window of 2L length, being it in position L+1, so that there are windows that are as many as the number of anchor points and are aligned and averaged to obtain the PRSA series itself. Those points that were reconstructed through linear interpolation are excluded from the anchor points.

Introducing PRSA series, s, and L into a specific equation will finally give AC if the PRSA is calculated for the accelerations or DC if vice versa PRSA is derived for decelerations.

Finally, deceleration reserve is calculated as a simple sum of DC and AC, knowing that, generally, we would aspect to have a positive value for DC and a negative value for AC.

A third folder containing the *"anamnesis"* parameters is uploaded in order to extract the neonatal post-partum parameters, hence pH, BE, and Apgar. These values, together with all the other parameters which are extracted for each subject, are reported into a structure, containing the name of the recording related to that subject, the CTG total signal, and the three sections of it, to check and record if one or more of them are ejected, the onset and offset points of accelerative and decelerative episodes, the RR series calculated on each of the three sections of signal, the corresponding values of AC and DC, the DR, the neonatal post-partum parameters. DR, pH, Apgar and BE are vectors of three values (or less, if some sections are excluded), for each subject.

Once verified that the row related to the subject is not empty, each DR vector is correlated to the neonatal post-partum parameters, though a function that gives as output two values: R is the

strength of the correlation and it is supposed to be as close as possible to -1 or +1; *p* is the statistical significance, which expresses the reliability of the correlation, if <0,05.

A scatter plot of each correlation is displayed, to graphically visualize a possible analog trend between each couple of parameters.

A further division of the subjects is done according to the values of each of the neonatal post-partum parameters. Following the criteria of the threshold values, to determine the occurrence of acidosis, which are reported in *Table 1*, for pH and BE, and in *Table 2* for Apgar score, we consider all the subjects where pH is <7.2, Apgar<7 and BE >-4 as acidosis positive, and the remaining subjects as negative cases.

Once this separation of the subjects in six groups, a positive and a negative group for each of the post-partum parameters, is accomplished, we calculate the DR value related to every of these groups. Being DR a vector of multiple values, it is easier to consider a single value that represents the Deceleration Reserve of the whole amount of subjects contained in each group, deriving it as the median value of the 25° and 75° percentile of each DR vector.

Finally, the control group, which is the negative one, and the positive group, are inserted in a *rank-sum* function, in order to apply a Wilcoxon rank-sum test, deriving the *p-value* for pH, Apgar and BE. This test is used to identify if there are significant statistical differences among the medians of the two vectors, depending on the fact that *p-value* is higher or lower than *alpha,* which is set to 0.05. If we find a small *p-value* (i.e. lower than *alpha*), we can conclude with a sufficient degree of confidence that there is evidence of a statistically significant difference between the medians of positive and negative pH group, positive and negative BE group and positive and negative Apgar group.

Results

From the total amount of subjects in the database of our interest, which were 552, 112 signals are excluded, remaining with 440 valid subjects.

After the division of each signal in three equal parts, giving a total of 1320 portions of signal, 102 of these portions of signal are eliminated for having a zero percentage higher than 10%.

Correlation between the deceleration reserve DR and the three neonatal post-partum parameters, in particular pH, BE, and Apgar, is expressed by two statistical parameters: R for the strength of the correlations, *p* for the significance of the correlations. The numerical values for each couple of correlated parameters are reported in *Table 8*. In *Figure 31*, a scatter plot represents the behaviour of the index DR, depending on pH, BE and Apgar.

Table 8. R and p-values for DR/ neonatal post-partum parameters correlation

		pH	BE	Apgar
DR	**R-value**	**0.05**	**-0.04**	**0.14**
DR	***p-value***	**0.09**	**0.14**	**$< 10^{-5}$**

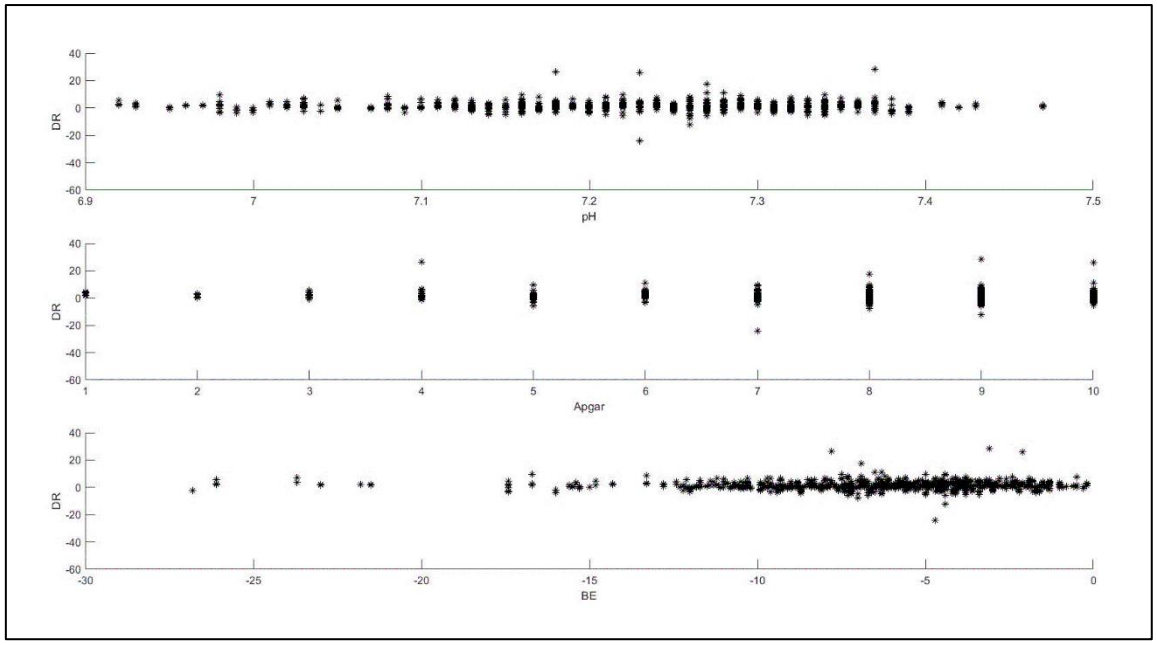

Figure 31. A scatter plot of DR, depending on each of the three neonatal post-partum parameters

Analysing the positivity to acidosis for each subject, according to pH, BE and Apgar values, we divided a total of 437/440 subjects in six groups, as stated in *Table 9*.

135 subjects present pH<7.2, while 104 subjects have BE >-4 and 57 have Apgar<7. On the contrary, 302 subjects for pH, 333 for BE and 380 for Apgar are considered negative and therefore healthy.

Table 9 also reports the 25° and 75° percentile DR and their median value for each of the six groups, as well as the *p-value* related to each couple of groups, which is related to each of the three post-partum neonatal parameters. All *p-values* result to be >0.05.

Table 9. Acidosis positive and negative groups for pH, BE and Apgar, with the related median DRs, calculated on the 25° and 75° percentiles of the DR vectors and the p-values from the Wilcoxon rank-sum test

	pH total (437/440 subjects)		**BE total (437/440 subjects)**		**Apgar total (437/440 subjects)**	
	pH+	**pH-**	**BE+**	**BE-**	**Apgar+**	**Apgar-**
number of subjects	**135**	**302**	**104**	**333**	**57**	**380**
25° percentile	**0.08**	**0.13**	**0.25**	**0.10**	**0.09**	**0.12**
75° percentile	**2.20**	**2.14**	**2.46**	**2.07**	**2.06**	**2.19**
median DR	**1.14**	**1.14**	**1.35**	**1.08**	**1.07**	**1.15**
p-value	**0.97**		**0.09**		**0.72**	

Discussion and conclusion

This study is conducted with the purpose to process and analyse CTG fetal recordings, with a particular focus on the presence of accelerations and decelerations of the fetal heart rate during labour, without distinction between healthy and pathological subjects. Further information about the foetal wellbeing after the delivery is available for each of these subjects, being expressed by pH, BE and Apgar score.

This study aims to find a correlation among these parameters and the CTG features, in order to predict the possible occurrence of foetal acidosis during labour, thought the examination of the CTG recording in an automatic way. Such procedure in fact, is still mostly left to the medical personnel's experience and subjective evaluation, despite the existence of general international guidelines. More in detail, we intent to identify the presence of a correlation between DR, which is the deceleration reserve, given by the sum of the acceleration and deceleration capacities, and three neonatal post-partum parameters, that are pH, BE and Apgar score.

We ejected from the analysis those subjects who do not present any acceleration and deceleration in their CTG recording or for whom we do not have information about their neonatal post-partum parameters, and we eliminated those parts of the signal which have a presence of zeros >10%, to have a clearer dataset to work with. Once verified the correlation between the DR and each of the three neonatal post-partum parameters, we expect to have two values as result: R, which expresses the strength of the correlation, meaning a strong correlation if close to -1 or 1, and *p-value*, which is related to a reliable statistical significance if <0.05. Our results show R values of 0.05 for the correlation DR/pH, -0.04 for DR/BE and 0.14 for DR/Apgar, values that are not close to either 1 or -1, expressing lack of correlation among these parameters, with the used approach. Also, *p-values* are 0.09 for DR/pH, 0.14 for DR/BE and $< 10^{-5}$ for DR/Apgar. So, this last correlation is the only one with a satisfying statistical significance, being the *p-value* lower than 0.05.

Moreover, according to the values of neonatal post-partum parameters for each subject, it is possible to determine the physiological states, separating them from the ones with pathological values of pH, BE, and Apgar. This results into a total set of 437 subjects, among which the positive subjects were identified as 135 subjects with pH <7.2, 104 with BE>-4 and 57 with Apgar score <7.

The DR of the positive and negative subjects, in relation with each of the post-partum parameters, are then used in a Wilcoxon rank-sum test, to obtain the *p-values.* The results of this test show *p-values* of 0.97 for the pH, 0.09 for the BE and 0.72 for the Apgar, which are

much higher that the alpha threshold of 0.05. This means that the hypothesis of a statistically significant difference between the medians of positive and negative pH group, positive and negative BE group and positive and negative Apgar group cannot be satisfied in this specific case.

These considerations lead to the idea that, using the approach described in this thesis, it is not possible to assess the presence of a reliable correlation between the DR and the neonatal post-partum parameters.

This could imply that the correlation could be found using a different method of analysis and evaluation of the parameters, which could be more appropriate for this specific case.

A possible deduction could also be related to the use of DR, which could be not appropriate for the aim of this study, as well as it would be possible to obtain better results using different parameters than the ones here considered, since we know that they are still related to a certain level of subjective interpretation.

The presence of correlation among CTG features and neonatal post-partum parameters is therefore not excluded, but it is left to future studies, considering the presence of limitations to overcome.

A potential future methodology could involve the introduction in the analysis of uterine contractions, that are known to interfere on the FHR and its features, since they are not evaluated in our present study.

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