



UNIVERSITÀ POLITECNICA DELLE MARCHE
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**Role of neonatal outcomes for fetal hypoxia
identification: heart rate variability analysis**

**Ruolo degli outcomes neonatali per
l'identificazione dell'ipossia fetale: analisi
della variabilità del ritmo cardiaco**

Relatore:

Dott.ssa Agnese Sbröllini

Tesi di Laurea di:

Udo-Chukwu Ifunanya Chukwu
Oruche

Correlatore:

Prof.ssa Laura Burattini

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ABSTRACT

La gravidanza rappresenta un complesso fenomeno biologico caratterizzato da una serie di intricate trasformazioni fisiologiche che culminano con la nascita di un neonato. Una comprensione completa di questo processo riveste importanza fondamentale per il benessere sia della madre in gravidanza che del neonato. Questa comprensione globale richiede un'esplorazione di diverse sfaccettature, che includono adattamenti nelle strutture anatomiche della madre, dinamiche di sviluppo fetale durante i trimestri, il discernimento e la gestione delle complicazioni specifiche di ciascun trimestre e le complesse fasi del travaglio, insieme alle sfide ad esse connesse.

Inoltre, un aspetto cruciale per valutare lo stato di salute sia della madre che del feto riguarda un'attenta analisi del sistema cardiaco fetale. La rappresentazione elettrocardiografica di questo sistema fornisce preziose informazioni sulla frequenza cardiaca fetale, una misura fondamentale per valutare il benessere del feto. Il principale obiettivo di questa tesi si concentra sull'indagine della variabilità della frequenza cardiaca fetale (FHRV) e sulle metodologie rigorose impiegate per la sua analisi.

Tra le numerose sfide legate alla gravidanza, l'ipossia fetale assume una notevole importanza a causa delle sue potenziali ripercussioni sul feto e sulla madre. La valutazione del benessere fetale, con particolare enfasi sulla rilevazione dell'ipossia fetale, può essere efficacemente ottenuta attraverso un'approfondita analisi della variabilità della frequenza cardiaca fetale. Questa tesi si propone di chiarire come l'esame della FHRV possa fungere da strumento diagnostico per l'identificazione dell'ipossia fetale.

Lo strumento fondamentale impiegato per monitorare il benessere fetale è la Cardiotocografia (CTG). La CTG non solo consente un esame completo delle dinamiche della frequenza cardiaca fetale, ma fornisce anche informazioni sulle contrazioni uterine. L'interpretazione dei vari modelli di tracciato CTG riscontrati durante il monitoraggio deve seguire linee guida stabilite.

L'obiettivo principale di questa tesi è determinare il parametro più pertinente tra il pH (che indica l'acidità o l'alcalinità di una soluzione), il BE (che indica l'eccesso o il deficit di sostanze alcaline nel sangue, offrendo informazioni sull'equilibrio chimico del corpo) e l'Apgar5 (utilizzato per valutare le condizioni fisiche del neonato) per valutare il benessere fetale. Per raggiungere questo obiettivo, è stata selezionata una coorte di 395 neonati dai database della Czech Technical University (CTU) di Praga e dell'Università di Brno (UHB). Questi neonati sono stati suddivisi in gruppi sani e patologici in

base a criteri specifici, tra cui $\text{pH} < 7.1$, $\text{Apgar5} < 7$ e $\text{BE} < -10 \text{ mmol/L}$. I neonati che soddisfacevano questi criteri sono stati considerati patologici, mentre quelli che non li soddisfacevano sono stati considerati sani. È importante notare che il pH e il BE sono parametri oggettivi, mentre l'Apgar5 è soggettivo.

Successivamente, dopo questa categorizzazione, sono stati presi in considerazione ulteriori parametri, come gli intervalli NN medi (che rappresentano la durata media degli intervalli normali tra battiti cardiaci successivi), la deviazione standard degli intervalli NN (che quantifica la variabilità complessiva di questi intervalli), la potenza a frequenza molto bassa, la potenza a bassa frequenza, la potenza ad alta frequenza, il rapporto tra bassa frequenza e alta frequenza e TINN (un parametro FHRV basato sul dominio temporale che descrive la forma complessiva dell'istogramma degli intervalli NN). Questi parametri sono stati esaminati per la loro capacità di distinguere tra soggetti patologici e sani, con l'obiettivo di valutarne l'adeguatezza come parametri diagnostici. Questi parametri sono stati selezionati in quanto comunemente utilizzati nella letteratura come misure standard per l'analisi della FHRV. È stato utilizzato il test U di Mann-Whitney a causa della distribuzione non normale di questi parametri, che li rende inadatti per i test di distribuzione normale convenzionali.

In seguito al test U di Mann-Whitney, è emerso che i parametri categorizzati in base all'Apgar5 non presentavano differenze statisticamente significative ($p > 0,05$) e sono stati quindi esclusi da ulteriori considerazioni. Per quanto riguarda il BE e il pH, tra i parametri statisticamente significativi, la deviazione standard degli intervalli NN si è rivelata un discriminante prominente. Tuttavia, la deviazione standard del pH è stata alla fine scelta come parametro più affidabile a causa del suo valore p inferiore a 0,05, a conferma di una significativa differenza tra i neonati patologici e quelli sani. In sostanza, l'uso della deviazione standard consente di comprendere il funzionamento del sistema nervoso autonomo e la sua influenza sulla frequenza cardiaca, facilitando così il riconoscimento dell'ipossia neonatale.

Questi risultati mettono in luce l'importanza di fare affidamento su parametri oggettivi per l'identificazione precisa dei casi patologici. Mentre i parametri soggettivi come l'Apgar5 hanno valori numerici, la loro valutazione è influenzata in modo significativo da fattori contestuali ed è soggetta alla soggettività umana.

Tuttavia, è fondamentale riconoscere che, nonostante il raggiungimento dell'obiettivo principale di questa tesi, le conclusioni potrebbero non essere del tutto

precise a causa del numero limitato di parametri statisticamente significativi. Questa limitazione potrebbe essere attribuita alla qualità del database, influenzata dalla presenza di dati mancanti dovuti a problemi di acquisizione.

ABSTRACT

Pregnancy represents a multifaceted biological phenomenon characterized by a cascade of intricate physiological transformations culminating in the birth of a neonate. A comprehensive comprehension of this process holds paramount importance for the well-being of both the expectant mother and the newborn. This comprehensive understanding necessitates an exploration of diverse facets, encompassing adaptations in maternal anatomical structures, fetal developmental dynamics across trimesters, the discernment and management of trimester-specific complications, and the intricate stages of labor, along with their concomitant challenges.

Furthermore, a pivotal facet in assessing the health status of both the mother and the fetus involves a meticulous scrutiny of the fetal cardiac system. The electrocardiographic representation of this system provides invaluable insights into fetal heart rate, a pivotal metric in evaluating fetal well-being. The primary focus of this thesis centers on the investigation of fetal heart rate variability (FHRV) and the rigorous methodologies employed for its analysis.

Among the myriad challenges intertwined with pregnancy, fetal hypoxia assumes considerable significance due to its potential repercussions on both the fetus and the mother. The evaluation of fetal well-being, with particular emphasis on the detection of fetal hypoxia, can be effectively achieved through an in-depth analysis of fetal heart rate variability. This thesis endeavors to elucidate how the examination of FHRV can function as a diagnostic tool for identifying fetal hypoxia.

The instrumental tool employed for monitoring fetal well-being is Cardiotocography (CTG). CTG not only facilitates a comprehensive examination of fetal heart rate dynamics but also offers insights into uterine contractions. The interpretation of diverse CTG trace patterns encountered during monitoring must adhere to established guidelines.

The primary objective of this thesis is to determine the most relevant parameter among pH (indicating the acidity or alkalinity of a solution), BE (indicating the excess or deficit of alkaline substances in the blood, offering insights into the body's chemical balance), and Apgar5 (utilized to assess the physical condition of the newborn) for assessing fetal well-being. To achieve this, a cohort of 395 neonates from the databases of the Czech Technical University (CTU) in Prague and the University Hospital in Brno (UHB) was selected. These neonates were categorized into healthy and pathological groups based on specific criteria, including $\text{pH} < 7.1$, $\text{Apgar5} < 7$, and $\text{BE} < -10 \text{ mmol/L}$. Neonates meeting these criteria were deemed pathological, while those not meeting them were

considered healthy. An essential consideration was that pH and BE are objective parameters, whereas Apgar5 is subjective.

Subsequently, after this categorization, additional features were considered, such as Mean NN intervals (representing the average duration of normal-to-normal intervals between successive heartbeats), Standard Deviation NN intervals (quantifying the overall variability in these intervals), Very Low Frequency Power, Low Frequency Power, High Frequency Power, Ratio of Low Frequency to High Frequency, and TINN (a time-domain FHRV parameter describing the shape of the histogram of NN intervals). These features were scrutinized for their potential to distinguish between pathological and healthy subjects, aiming to ascertain their suitability as diagnostic features. These features were selected due to their prevalence in the literature as standard measures for FHRV analysis. The utilization of the Mann-Whitney U test was necessitated by the non-normal distribution of these features, rendering them unsuitable for conventional normal distribution tests.

Subsequent to the Mann-Whitney U test, it was observed that the features categorized based on Apgar5 did not exhibit statistical significance ($p > 0.05$) and were therefore excluded from further consideration. Regarding BE and pH, among the statistically significant features, Standard Deviation NN intervals emerged as a prominent discriminator. However, the Standard Deviation of pH was ultimately chosen as the most reliable parameter due to its lower p-value (less than 0.05), signifying a significant difference between pathological neonates and their healthy counterparts. In essence, the utilization of Standard Deviation enables the understanding of the autonomic nervous system's function and its influence on heart rate, thereby aiding in the recognition of neonatal hypoxia.

These findings underscore the significance of relying on objective parameters for the precise identification of pathological cases. While subjective parameters like Apgar5 possess numerical values, their assessment is substantially influenced by contextual factors and is susceptible to human subjectivity.

Nevertheless, it is imperative to acknowledge that despite achieving the primary objective of this thesis, the conclusion may not be entirely precise due to the limited number of statistically significant features. This limitation could potentially be attributed to the database's quality, influenced by the presence of missing data resulting from acquisition challenges.

Contents

INTRODUCTION.....	I
CHAPTER 1: PREGNANCY	1
1.1 <i>Anatomy of Pregnancy</i>	1
1.2 <i>Fetal Development</i>	4
1.3 <i>Fetal Cardiovascular System</i>	13
1.3.1 <i>Electrical activity of the heart</i>	20
1.3.2 <i>Normal and Abnormalities of FHR</i>	24
1.4 <i>Fetal Hypoxia</i>	28
CHAPTER 2: CARDIOTOCOGRAPHY	30
2.1 <i>Classification of Traces.....</i>	35
2.2 <i>Guidelines for Cardiotocography traces</i>	43
CHAPTER 3: FETAL HEART RATE VARIABILITY	45
3.1 <i>Techniques Analysis</i>	47
3.1.1 <i>Time Domain Analysis</i>	47
3.1.2 <i>Frequency Domain Analysis</i>	50
3.1.3 <i>Nonlinear Techniques.....</i>	55
3.2 <i>Fetal Heart rate and Hypoxia.....</i>	59
CHAPTER 4: ANALYSIS OF HEART RATE VARIABILITY	62
4.1 <i>Data</i>	62
4.2 <i>Method</i>	63
4.3 <i>Results.....</i>	64
4.4 <i>Discussion</i>	68
CONCLUSIONS	II
APPRECIATION	IV
BIBLIOGRAPHY	V

INTRODUCTION

Optimal maternal health and normal placental development are pivotal for embryogenesis, fetal growth, and the survival of the perinatal period. Disruption in these processes due to maternal exposure to persistent hypoxia can lead to critical organ injuries, jeopardizing the well-being of both the mother and the developing fetus. Consequences of impaired placental function include intrauterine growth restriction (IUGR), asphyxia, multiorgan failure, premature delivery, and perinatal demise. In the United States, IUGR and prematurity complicate approximately 12% of deliveries, constituting the leading causes of perinatal mortality and morbidity, contributing to up to 75% of perinatal deaths. These adverse outcomes, along with associated long-term disabilities such as cerebral palsy, hearing loss, retinopathies, and chronic lung disease, place a substantial emotional and economic burden on affected families and society at large.

Fetal hypoxia, characterized by inadequate oxygen supply to the developing fetus, is a condition that poses a significant threat to fetal development and increases the risk of perinatal and infant mortality. It accounts for 23% of neonatal deaths worldwide, with numerous risk factors such as placental insufficiency, pre-eclampsia, umbilical cord damage, and maternal conditions such as smoking, heart, kidney, or lung dysfunction contributing to its occurrence.

Prenatal hypoxia can be categorized into three patterns: pre-placental, uteroplacental, and post-placental, with the latter two being particularly relevant to the direct impact of hypoxia on the fetus. Fetal hypoxia triggers the production of reactive oxygen species (ROS), which, while essential for various cellular functions, become detrimental when their production exceeds the capacity of antioxidant defenses. In the placenta, ROS-induced DNA damage, protein denaturation, and lipid peroxidation can alter placental function, leading to reduced oxygen and nutrient delivery to the fetus. This sequence of events results in limited fetal growth, low birth weight, and alterations in the offspring's body shape. Furthermore, growth restriction often coincides with abnormal organ development, potentially giving rise to organs ill-equipped for proper function in later life.

Exposure to short bouts of fetal hypoxia prompts a redistribution of blood flow, prioritizing essential circulation to protect the brain and heart. However, prolonged intrauterine hypoxia can compromise initial homeostatic defenses, placing undue stress on the developing heart and primary vessels, ultimately impacting fetal heart function and cardiac gene expression. This not only poses immediate

risks to fetal life but also predisposes the offspring to congenital anomalies and chronic diseases, such as cardiovascular, renal, and metabolic disorders in later life.

Therapeutic interventions during pregnancy hold promise as an avenue to mitigate the harmful effects of fetal hypoxia-induced oxidative stress.

This thesis aims to provide a comprehensive overview of both preclinical and clinical evidence linking fetal hypoxia to oxidative stress. Specifically, we will focus on the correlation between fetal hypoxia and heart rate variability (HRV) analysis, seeking to determine which HRV parameters are most relevant for identifying fetal hypoxia.

CHAPTER 1: PREGNANCY

1.1 Anatomy of Pregnancy

During pregnancy, remarkable physiological changes occur in the female body to support the growth and development of the fetus. Two critical components of this process are the uterus and placenta, both of which undergo intricate modifications to ensure the well-being of both mother and child.[1]

The uterus experiences significant alterations in terms of weight and volume throughout pregnancy. In its nonpregnant state, the uterus typically weighs between 4 to 70 g and has a volume of around 10 ml. However, by the time of delivery, it can expand to a weight ranging from 1100 to 1200 g and a volume of approximately 5 l. These changes primarily result from the hypertrophy, or enlargement, of existing myometrial cells, primarily driven by the influence of estrogen. Moreover, there is an increase in fibrous and connective tissue, blood vessels, and lymphatics within the uterus, contributing to its growth. Notably, the lower uterine segment, or isthmus, becomes thinner and more distensible, serving a distinct role in the childbirth process. [1]

Concomitant with these uterine changes is a substantial increase in uterine blood flow. Blood flow to the uterus rises from 2% of cardiac output in the nonpregnant state to 17% at term. This augmented blood flow is distributed unevenly within the uterus, with the majority directed towards the placenta, essential for fetal nourishment. The remaining blood flow is shared between the endometrium and myometrium. Estrogen plays a key role in influencing vascular changes within the uterus, leading to reduced resistance in placental vasculature and increased blood flow. [1]

The specific cellular mechanisms governing the increase in uteroplacental blood flow are not fully elucidated; however, several hormones, including vascular endothelial growth factor, angiotensin II, nitric oxide, and prostacyclin, likely contribute to the regulation of uterine blood flow. These intricate changes in the uterus and its vasculature are critical for supporting the developing placenta and meeting the nutritional and oxygen requirements of the growing fetus during pregnancy. [1]

The placenta, another pivotal component of pregnancy, also undergoes significant modifications to facilitate the exchange of essential substances between the mother and the fetus. Acting as an interface, the placenta enables the transfer of gases, nutrients, and various molecules through a combination of osmotic, hydrostatic, and diffusion forces. [2]

Respiratory gases, such as oxygen and carbon dioxide, move across the placenta primarily due to partial pressure gradients between maternal and fetal circulations. The placenta's efficiency in gas

exchange allows for equilibrium between oxygen and carbon dioxide levels, although variations may occur in different compartments due to blood flow distribution. [2]

Nutrient transfer, crucial for fetal growth and development, is facilitated by specific transport proteins present on placental membranes. These transporters ensure efficient transport of substances like glucose, amino acids, and fatty acids, while protecting against potentially harmful compounds. [2]

Water and ions also traverse the placenta through a combination of osmotic, hydrostatic, and colloid osmotic forces, with the involvement of specific water channels called aquaporins. Mechanisms such as sodium transporters, chloride channels, and calcium transport proteins regulate ion and water movement across the placenta. [2]

Additionally, the placenta functions as an endocrine organ, producing hormones such as human chorionic gonadotropin (hCG), human placental lactogen (hPL), and placental growth hormone (PGH). These hormones play vital roles in sustaining pregnancy, supporting fetal growth, and regulating maternal physiology. [2].

Furthermore, the cardiovascular system also undergoes substantial adjustments during pregnancy to optimize oxygen delivery to both the mother and fetus. These adaptations encompass changes in cardiac structure and function, leading to a significant increase in cardiac output (CO). CO rises by 30% to 50% above pre-pregnancy levels, peaking around 25 to 30 weeks of gestation, with the uterus, placenta, and breasts receiving most of the increased blood flow. This increase in CO is attributed to both an elevation in stroke volume (SV) and heart rate (HR), with HR peaking around 32 weeks and SV reaching its maximum at approximately 20 weeks. Maternal position can influence CO, with variations noted in different postures, including supine hypotension in some cases due to inferior vena cava compression by the uterus. [2]

To address these CO changes, systemic vascular resistance (SVR) compensates to maintain blood pressure, ensuring adequate perfusion to vital organs. Interestingly, twin pregnancies exhibit higher CO levels compared to singleton pregnancies.[2]

Simultaneously, in the respiratory system, hormonal shifts, particularly increased estrogen levels, lead to upper respiratory tract changes, including nasal congestion, rhinitis, and epistaxis. Mechanical adaptations in the thoracic cage, such as an increased subcostal angle, chest expansion, and diaphragm elevation, affect lung volumes, with total lung capacity (TLC), functional residual capacity (FRC), expiratory reserve volume (ERV), and residual volume (RV) undergoing alterations.

Progesterone-induced chronic hyperventilation results in modifications in tidal volume, minute ventilation, and alveolar ventilation, affecting oxygen and carbon dioxide levels. Maternal oxygen consumption rises, particularly during exertion and labor, while sleep patterns are significantly disrupted, leading to changes in sleep stages and quality.[2]

The urinary system also experiences substantial changes during pregnancy, driven by the increased cardiac output. These changes result in a 50% increase in glomerular filtration rate (GFR) and up to an 80% increase in renal plasma flow (RPF). The elevated GFR leads to decreased levels of creatinine, urea, and uric acid in the blood. Kidneys undergo enlargement and physiological hydronephrosis due to fluid retention. Additionally, hormonal influences relax the smooth muscles of the urinary collecting system, potentially leading to urinary stasis and an increased risk of urinary tract infections and pyelonephritis. [2]

Moreover, the renin-angiotensin-aldosterone system (RAAS) experiences upregulation during pregnancy, with increased levels of aldosterone contributing to a net gain of approximately 1.5l of water. These adaptations are essential for maintaining maternal and fetal well-being. [2]

In the gastrointestinal system, multiple factors contribute to the occurrence of gastroesophageal reflux disease (GERD) in pregnant individuals. Increased progesterone levels result in decreased resting muscle tone of the lower esophageal sphincter (LES), delayed gastric emptying, and prolonged transit time in the small bowel. These changes, combined with the pressure exerted by the growing uterus, make pregnant women more susceptible to GERD. [2]

1.2 Fetal Development

According to the site “birth injury help centre” and National Institutes of Health (NIH), pregnancy is a term used to talk about how the fetus developed in the womb or in the uterus. Typically lasting about 40 weeks, pregnancy is divided into three trimesters, which correspond to different stages of the fetus growth.

In the First Trimester, during weeks 1 to 12, the mother's body undergoes significant hormonal changes. Early symptoms include fatigue, breast tenderness and swelling, nausea (with or without vomiting), food cravings or aversions, mood swings, constipation, frequent urination, headaches, and weight fluctuations.

Meanwhile the vital organ development of the fetus takes place. By the end of this period, all the baby's organs should be formed, in particular:

Weeks 1 & 2: Conception occurs approximately two weeks after the start of the last menstrual cycle. Although not technically pregnant during these weeks, healthcare professionals count from the last menstrual cycle to determine the duration. Miscarriages caused by a blighted ovum are common during this stage.

Week 3: Fertilization takes place in the fallopian tubes, resulting in a one-celled entity called a zygote. Multiple eggs may be fertilized, or the fertilized egg may split, leading to multiple zygotes. The zygote develops into a cluster of cells called a morula, which then travels to the uterus for implantation.

Week 4: Implantation occurs as the blastocyst (formerly morula) burrows into the uterine lining. The blastocyst consists of cells that will develop into the embryo and the outer layer that forms the placenta.

Week 5: hCG hormone levels rise rapidly, causing the ovaries to stop releasing eggs and increasing estrogen and progesterone production. The embryo develops three distinct layers: the ectoderm, mesoderm, and endoderm, which give rise to different body systems.

Week 6: Rapid growth occurs, and the neural tube along the baby's back begins to close, setting the stage for brain and spinal cord development. Other organs and structures, such as the heart, eyes, ears, and limbs, start to form.

Week 7: The baby's brain and face continue to grow, with the nostrils, eyes, legs, and arms becoming visible.

Weeks 8 through 12: During this period, the baby's features become more defined, and various body parts, such as the nose, toes, arms, eyes, eyelids, genitals, and fingernails, form. By week 11, the baby is officially considered a fetus. At week 12, the intestines move into the abdomen, and the fetus measures around 2.5 inches and weighs approximately half an ounce.

It is crucial for expectant mothers to maintain a healthy diet during the first trimester, ensuring an adequate intake of folic acid to prevent neural tube defects. To minimize the risk of miscarriage, it is important to take prenatal vitamins, avoid smoking, alcohol, drugs (including certain prescription medications), and make dietary changes such as reducing caffeine intake and avoiding deli meats and shellfish. Smoking and consuming drugs or alcohol during pregnancy can lead to serious complications and birth defects, necessitating their cessation.

Other complications to be aware of during the first trimester include bleeding, hyperemesis gravidarum (excessive vomiting), spontaneous abortions or miscarriages, ectopic pregnancies, and molar pregnancies.

Bleeding is a common occurrence in the first trimester, usually in the form of minimal bleeding or spotting. Although it can be challenging to determine the severity of bleeding, it should generally be taken seriously unless otherwise advised by a physician. In certain cases, bleeding may indicate a potential miscarriage, and if vaginal bleeding occurs, it is essential to consult a physician to rule out serious underlying issues.

Hyperemesis gravidarum, characterized by severe vomiting, is primarily experienced in the first trimester due to the presence of the beta human chorionic gonadotropin (B-hCG) hormone. This pregnancy hormone stimulates the brain's CTZ center, triggering vomiting. While vomiting is a common occurrence during pregnancy, persistent and severe vomiting can hinder proper nutrition and fluid intake, posing risks to both the mother and the baby. Seeking appropriate medical treatment is crucial if persistent and excessive vomiting is experienced.

Spontaneous abortion or miscarriage refers to the natural termination of pregnancy before the point of viability. Women with no prior history of spontaneous abortions have a roughly 15% chance of experiencing one, although the risk increases if they have had previous miscarriages. Symptoms to watch for include lower abdominal cramps accompanied by a backache, vaginal bleeding or discharge, uterine contractions, and nausea or vomiting. Various factors can contribute to spontaneous

abortions, such as chromosomal abnormalities, endocrine causes (including progesterone hormone deficiencies and uncontrolled diabetes), infections, and abnormal placental implantation.

Ectopic pregnancy occurs when the fertilized egg implants outside the uterine cavity, most commonly in the fallopian tube. This condition is considered a medical emergency and requires prompt attention. Key signs to watch for include lower abdomen pain on either side, sudden onset of cramping, possible fainting, repeated episodes of severe abdominal pain, vaginal bleeding, increased urinary frequency with a burning sensation, multiple missed periods, and fever. Early detection and appropriate treatment, including surgery, if necessary, can help resolve many cases of ectopic pregnancies.

A molar pregnancy results from abnormal development of cells in the placenta that cannot support the growth of an embryo. Chromosomal abnormalities in the sperm, egg, or both can contribute to molar pregnancies. Certain factors, such as advanced maternal age (over 40 years), specific ethnicities (Asians and African Americans have higher incidence rates), malnourishment, protein deficiencies, and previous occurrences of molar pregnancies, can increase the risks. Symptoms to be watchful for include irregular periods for three to four months, brown or prune-colored bleeding, and excessive vomiting.

In the Second Trimester, occurring from week 13 to week 28, the second trimester brings relief from symptoms like nausea and fatigue. Instead, women may experience a growing abdomen, body aches, stretch marks, dark patches of skin on the face, carpal tunnel syndrome, itching, and swelling in the ankles, fingers, and face. Most women find this trimester easier and will feel their baby's movements. The baby can also hear and recognize the mother's voice during this time.

By week 13, major organ formation is complete, but the fetus is still not developed enough to survive outside the womb. Gender may be visible around week 14, and mothers might feel fetal movement, known as quickening, during week 15.

During the second trimester, it is important for mothers to consider undergoing screening tests based on their medical and family history, as well as any potential genetic issues that could pose risks to the baby. An anatomy ultrasound is also recommended to assess the proper functioning of the baby's heart, lungs, kidneys, and brain.

Gestational diabetes, which can develop between weeks 26 and 28, is another concern during this trimester. Testing is done to ensure that the mother's body is responding appropriately to sugar during pregnancy.

While the risk of miscarriage decreases in the second trimester, there are still potential complications to be aware of. Infections or abnormalities of the uterus or placenta can increase the risk of miscarriage. One common complication is an incompetent cervix, where the cervix is weak and soft, and may open too early. As the baby grows and exerts pressure, the cervix may dilate and shorten prematurely, leading to a miscarriage, preterm delivery, or early rupture of the membranes. Early detection of an incompetent cervix allows for interventions that can significantly reduce the risks of miscarriage or preterm delivery.

Placental abruption is another common complication during the second trimester. It occurs when the placenta separates from the uterus prematurely, and if more than half of the placenta detaches, a miscarriage becomes possible. Factors such as abdominal trauma, drug use, alcohol consumption, and smoking significantly increase the risk of placental abruption. Symptoms to watch for include bleeding and cramping or tenderness of the uterus.

The third trimester extends from week 29 until delivery. The baby continues to grow and develop, and the mother experiences further changes in her body. The duration and complications of the third trimester vary, and it's essential to monitor the baby's movements and attend regular check-ups to ensure a safe and healthy delivery.

During the third trimester, there are several important complications to be aware of that can impact both the mother and the baby.

Gestational diabetes is a condition that can develop during this period, leading to high blood sugar levels. It is important to control gestational diabetes through diet, exercise, and medication to minimize the risk of complications during birth. Usually, blood sugar levels return to normal after delivery. However, it's important to note that a history of gestational diabetes increases the risk of developing type 2 diabetes in the future.

Preeclampsia is another complication to be cautious of during the third trimester. It is characterized by high blood pressure and can cause damage to organs such as the liver and kidneys. The only cure for preeclampsia is the delivery of the baby, and if left untreated, it can lead to serious and potentially life-threatening complications for both the mother and the baby.

Preterm labor, which occurs when the body prepares for birth too early (before three weeks prior to the due date), is another concern. While preterm labor may lead to premature delivery, there are treatments available that can help delay or prevent it.

Preterm rupture of membranes is when the amniotic sac surrounding the baby ruptures before 37 weeks of pregnancy. This condition increases the risk of infection and premature delivery.

Placenta previa is a condition where the placenta covers the opening of the cervix. It is more common in women who have had previous cesarean sections or uterine surgeries. Smoking also significantly increases the risk of developing placenta previa.

Intrauterine growth restriction is a condition in which the fetus does not grow at the normal rate, resulting in a smaller-than-expected baby. This condition can lead to various problems, including low birth weight, difficulty handling the stress of delivery, reduced oxygen levels, hypoglycemia, a compromised immune system, abnormalities in body temperature, and high red blood cell counts. Intrauterine growth restriction can often be managed, but in severe cases, it can result in long-term growth problems in the child or even stillbirth.

Post-term pregnancy is a complication where the baby has not been born after 42 weeks. This condition carries risks for both the mother and the infant and is typically treated by inducing labor.

Labor is the biological process by which the fetus and placenta are expelled from the uterus through the vagina. The entire labor process in humans is divided into three distinct stages. The first stage is further subdivided into two phases. Successful labor requires the harmonious interaction of three crucial factors: maternal efforts and uterine contractions, fetal characteristics, and the anatomy of the maternal pelvis. These three factors are often referred to as the "passenger, power, and passage" triad.[2]

To ensure the well-being of both the mother and the baby during labor, medical professionals utilize various monitoring techniques. Serial cervical examinations play a vital role in monitoring the progress of labor. These examinations allow clinicians to assess cervical dilation (the opening of the cervix), effacement (the thinning of the cervix), and the fetal position within the birth canal, which is referred to as the station. [2]

Continuous fetal heart monitoring is an integral part of labor management. By continuously monitoring the fetal heart rate, clinicians can assess the baby's well-being and detect any signs of distress or abnormal heart patterns that may require immediate intervention.

Upon arrival at the obstetrical triage, women often self-present with concerns about the start of labor. They commonly report symptoms such as painful contractions, vaginal bleeding or a "bloody show," and fluid leakage from the vagina. The clinician's task is to determine if the patient is indeed in labor, which is defined as experiencing regular and clinically significant contractions with objective changes in cervical dilation and/or effacement.[2]

When a woman first arrives at the labor and delivery unit, the clinician conducts a thorough initial evaluation. Vital signs, including temperature, heart rate, oxygen saturation, respiratory rate, and blood pressure, are assessed and checked for any abnormalities. Continuous cardiotocographic monitoring is initiated to ensure the well-being of the fetus during the assessment process. [2]

The patient's prenatal record is carefully reviewed, encompassing obstetric history, surgical history, medical history, and any relevant laboratory and imaging data. This comprehensive review helps provide essential context for the current situation. [2]

Furthermore, a detailed history of the present illness is obtained, seeking specific information about the onset and progression of symptoms, contractions, and any other relevant factors. A review of systems is also performed to assess for any additional symptoms or concerns. Additionally, a physical examination is conducted, which may include a sterile speculum exam to check for signs of ruptured membranes (amniotic fluid leakage) and to assess cervical dilation and effacement. [2]

Overall, this comprehensive initial evaluation enables the clinician to accurately determine the patient's status and whether she is in active labor. It ensures that appropriate monitoring and interventions can be initiated promptly to ensure the safety and well-being of both the mother and the baby. [2]

The management of normal labor requires striking a delicate balance between allowing the natural process to unfold while being prepared to address potential complications that may arise. While labor is a natural phenomenon, certain factors may necessitate clinical intervention to ensure the safety and well-being of both the mother and the baby.[2]

During labor, continuous cardiotocographic monitoring is commonly employed to closely monitor uterine contractions and the fetal heart rate over time. This monitoring allows clinicians to assess for any signs of fetal distress that may require immediate intervention. Additionally, the adequacy of uterine contractions is evaluated to ensure effective progress in labor. Vital signs of the mother are regularly checked, and any changes in her clinical status are promptly addressed.[2]

Routine laboratory testing often includes assessments of hemoglobin, hematocrit, and platelet count. These tests may be repeated following delivery, especially in cases of significant blood loss. Cervical examinations are typically conducted every 2 to 3 hours, unless concerns arise that warrant more frequent assessments. Frequent cervical exams should be approached with caution, as they are associated with an increased risk of infection, particularly if the membranes have ruptured.

Women in labor are encouraged to freely ambulate and change positions as desired, as this can aid in the progress of labor and provide comfort. To ensure quick access in case of the need for medications or fluids, an intravenous catheter is typically inserted. Oral intake should not be unnecessarily restricted, but if a prolonged period without food or drink is anticipated, intravenous fluids may be considered to prevent dehydration.[2]

Pain management options are offered to women based on their individual needs and preferences. These options may include intravenous opioids, inhaled nitrous oxide, or neuraxial analgesia (such as epidural). The use of amniotomy (breaking of the water) is considered on an as-needed basis, for purposes like fetal scalp monitoring or labor augmentation, but its routine use is discouraged to minimize potential risks.[2]

When contractions are found to be inadequate for progressing labor, oxytocin may be administered to augment them and support the natural labor process. Overall, the management of normal labor involves a comprehensive approach that ensures the best possible outcomes for both the mother and the baby, while respecting the natural course of labor.[2]

The first stage of labor marks the beginning of labor until full cervical dilation reaches 10 cm, signifying its completion. Labor can commence spontaneously or may be medically induced due to various maternal or fetal indications. Induction methods include cervical ripening using prostaglandins, membrane stripping, amniotomy (breaking the amniotic sac), and intravenous oxytocin administration. Although pinpointing the exact start of labor can be imprecise, it is generally considered to begin when contractions become strong and occur at regular intervals, typically spaced around 3 to 5 min apart.[2]

During pregnancy, women may experience painful contractions that do not lead to cervical dilation or effacement, commonly known as false labor. This phenomenon makes it challenging to precisely determine the onset of true labor, often requiring retrospective or subjective evaluation. Early studies by Friedman et al. delved into labor progress and identified the commencement of labor as the point

when women experienced significant and regular contractions. By graphing cervical dilation over time, they observed that normal labor follows a sigmoidal pattern, presenting three distinct phases. The first phase, known as the latent phase, is characterized by slow cervical dilation, and accompanied by significant biochemical and structural changes. The second phase, called the active phase, is notably shorter and involves rapid cervical dilation. The third phase, referred to as the pelvic division phase, occurs during the second stage of labor.[2]

The second stage of labor commences once the cervix is fully dilated to 10 cm and concludes with the delivery of the neonate. This phase was also described as the pelvic division phase by Friedman. Once complete cervical dilation is achieved, the fetus begins its descent into the vaginal canal, whether maternal pushing efforts are involved. The process of the fetus passing through the birth canal involves seven essential movements known as the cardinal movements, which include engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion. [1,2]

The duration of the second stage of labor can vary based on individual factors. Women who have previously delivered vaginally and whose bodies have acclimated to the birthing process may experience a relatively short second stage, requiring only a brief trial. On the other hand, nulliparous women (first-time mothers) might have a longer second stage. [2]

The duration of the second stage of labor can also be influenced by whether neuraxial anesthesia (epidural or spinal anesthesia) is used. In parturients without neuraxial anesthesia, the second stage typically lasts less than three hours for nulliparous women and less than two hours for multiparous women. In contrast, for women who receive neuraxial anesthesia, the second stage usually lasts less than four hours for nulliparous women and less than three hours for multiparous women. [2]

If the second stage of labor surpasses these time parameters, it is considered prolonged. Several factors may contribute to the duration of the second stage. Fetal factors such as the size and position of the fetus, as well as maternal factors like the shape of the pelvis, the strength of expulsive efforts, and comorbidities such as hypertension or diabetes, can all play a role. Additionally, maternal age and history of previous deliveries may also influence the duration of the second stage of labor. [2]

The third stage of labor begins after the successful delivery of the fetus and concludes with the delivery of the placenta. The separation of the placenta from the uterine wall is characterized by three cardinal signs: a sudden gush of blood at the vagina, lengthening of the umbilical cord as it detaches

from the placenta, and a palpable globular-shaped uterine fundus (the top part of the uterus) during examination. [2]

In most cases, the placenta is spontaneously expelled within a period of 5 to 30 min after the baby's birth. However, if the placenta does not deliver within 30 min, there is an increased risk of postpartum hemorrhage, which is excessive bleeding after childbirth. In such situations, manual removal of the placenta or other medical interventions may be necessary to prevent further complications.[2]

The management of the third stage of labour involves facilitating the prompt delivery of the placenta. This is achieved by applying gentle traction to the umbilical cord while simultaneously exerting pressure on the uterine fundus. This process helps expedite the placental separation and ensures its safe delivery.

By effectively managing the third stage of labour, healthcare providers can minimize the risk of postpartum complications and promote a smooth recovery for the mother after childbirth.

1.3 Fetal Cardiovascular System

The development of the heart and vascular system begins during the third week after fertilization, originating from splanchnic mesoderm. In the fourth week, the two primitive heart tubes merge to form a basic contractile tube, marking the establishment of the cardiovascular system as the first functional organ system. From weeks 5 to 8, this single-lumen tube undergoes cardiac looping, remodelling, and partitioning processes to transform into the definitive four-chambered heart. However, during fetal life, there is a crucial opening called the foramen ovale in the interatrial septum that acts as a significant right-to-left shunt. [3]

By the fourth week of embryonic development, the vascular system exhibits three primary circulations. The aortic/cardinal circulation serves the developing embryo and forms the basis for much of the fetal circulatory system. Notably, the left sixth aortic (pulmonary) arch connects the left pulmonary artery to the aorta, forming the ductus arteriosus. The ductus arteriosus also functions as a right-to-left shunt by redirecting the output from the right ventricle to the aorta and the fetal/placental circulations. [3]

The vitelline circulation develops in conjunction with the yolk sac and, while it plays a minor role in nourishing the embryo, its reconfiguration ultimately establishes the circulatory system for the gastrointestinal (GI) tract, spleen, pancreas, and liver. The allantoic circulation emerges alongside the chorion and the developing chorionic villi, forming the placental circulation. It consists of two umbilical arteries and two umbilical veins. In humans, the venous pathways undergo reorganization between the fourth and eighth embryonic weeks, resulting in the retention of only the left umbilical vein. Subsequent restructuring of the vascular plexus associated with the developing liver gives rise to the ductus venosus, a venous shunt that diverts a significant portion of umbilical blood flow (approximately 70 to 130 ml/min/kg fetal weight after 30 weeks' gestation) bypassing the liver and entering the inferior vena cava. [3]

During placental gas exchange, well-oxygenated blood from the placenta exits through the umbilical vein. Apart from the ductus venosus, small branches supply the left lobe of the liver, while a major branch goes to the right lobe, accounting for the remaining umbilical venous flow. The oxygenated blood from the left hepatic vein combines with the flow from the ductus venosus as it enters the inferior vena cava. In contrast, the right hepatic vein combines with the portal vein, resulting in less oxygenated blood compared to its left counterpart. Furthermore, a mixture of right hepatic/portal drainage and blood returning from the lower trunk and limbs further reduces the oxygen content.

Although both the ductus venosus blood and hepatic portal/fetal trunk blood enter the inferior vena cava and the right atrium, minimal mixing occurs. The valve of the inferior vena cava and the crista dividens on the right atrium's wall guide the well-oxygenated blood from the ductus venosus preferentially into the foramen ovale, bypassing mixing with the superior vena cava/coronary sinus venous return. Consequently, the left atrium receives blood primarily from the umbilical vein-ductus venosus pathway, with a minor contribution from pulmonary venous flow. Thus, the left atrium and left ventricle receive highly oxygenated blood, supplying the upper body, limbs, carotid and vertebral circulations, and the brain. The flow from the inferior vena cava exceeds the capacity of the foramen ovale to accommodate it. The remaining oxygenated blood from the inferior vena cava passes through the tricuspid valve into the right ventricle, accompanied by venous return from the superior vena cava and coronary sinus. However, the pulmonary circulation's high vascular resistance maintains the mean pulmonary artery pressure slightly higher than the aortic pressure, directing most of the right ventricle's output through the ductus arteriosus into the aorta and the fetal/placental circulations. (Figure 1.1) [3]

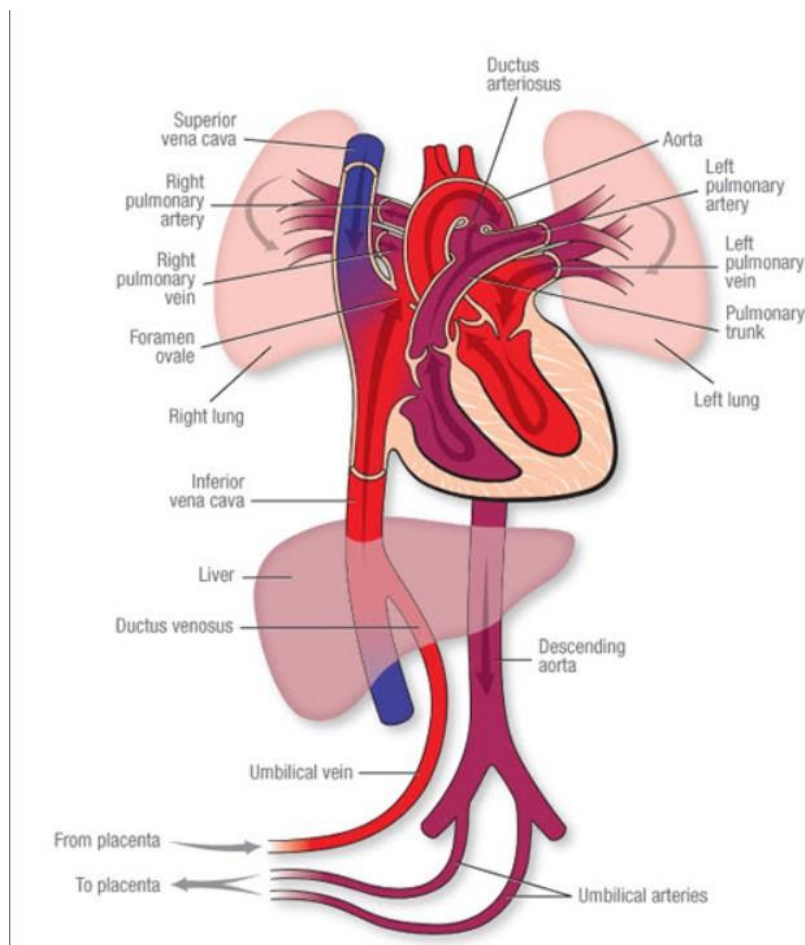


Figure 1.1: Fetal Heart and Circulation

The adult cardiovascular system consists of a high-pressure system (95 mm Hg) and a low-pressure pulmonary circuit (15 mmHg) driven by the left and right ventricles functioning in series. Despite the left ventricle having a higher ejection velocity than the right ventricle, equal volumes of blood are delivered to the systemic and pulmonary circulations with each ventricular contraction. The stroke volume refers to the volume of blood ejected by the left ventricle during each contraction, and cardiac output is determined by the stroke volume and heart rate (e.g., $70 \text{ ml/beat} \times 72 \text{ beats/min} = 5040 \text{ ml/min}$). In an average adult man weighing 70 kg, the cardiac output is around 72 ml/min/kg. Factors such as venous return (preload), pulmonary artery and aortic pressures (afterload), and contractility influence changes in stroke volume, which, in turn, affect cardiac output. [3]

In contrast to the adult heart, where the two ventricles pump blood in a series circuit, the fetal cardiovascular system has unique shunts that result in an unequal distribution of venous return to the respective atria. Consequently, ventricular output in the fetus represents a mixture of oxygenated and deoxygenated blood. The fetal right and left ventricles operate as two parallel pumps rather than in series, and the combined ventricular output describes the cardiac output. More than 60% of the combined ventricular output comes from the right ventricle and is primarily directed through the ductus arteriosus to the descending aorta. Thus, placental blood flow, accounting for approximately 40% of the combined ventricular output, predominantly reflects the output from the right ventricle. Due to the high pulmonary vascular resistance, only 5% to 10% of the combined ventricular output reaches the pulmonary circulation. The left ventricular output is mainly directed to the upper body and head through the aortic semilunar valve and aortic arch. The average fetal left ventricular output is estimated to be 120 ml/min/kg body weight. If the left ventricular output is less than 40% of the combined biventricular output, the total fetal cardiac output would exceed 300 ml/min/kg. The distribution of cardiac output to fetal organs is summarized in Table 1.1, with the fetal liver receiving blood supply mainly from the umbilical vein and to a lesser extent from the portal vein. The placenta receives approximately 40% of the combined ventricular output, which corresponds to the volume conducted by the single umbilical vein. About half of the umbilical venous blood bypasses the liver through the ductus venosus, while the rest traverses the hepatic circulation. The combination of umbilical vein blood, hepatic portal blood, and blood returning from the lower body contributes to approximately 69% of the cardiac output entering the right atrium through the inferior vena cava. The foramen ovale accounts for about one third (27%) of the combined cardiac output, and pulmonary venous return to the left atrium represents approximately 7% of the combined ventricular output. Consequently, the left atrium receives only about 34% (27% + 7%) of the combined ventricular output.

A volume equivalent to 27% of the combined ventricular output is shunted across the foramen ovale, while 42% remains in the right atrium and contributes to the output of the right ventricle. The right ventricular output constitutes 66% of the combined ventricular output, with only 7% entering the pulmonary circulation and the remaining 59% entering the aorta through the ductus arteriosus. Similarly, 24% of the combined ventricular output derived from the left ventricle is distributed to the upper body and brain, with approximately 10% combining with the right ventricular output in the aorta. Thus, 69% of the combined ventricular output reaches the descending aorta, of which 40% is directed to placental flow, while the rest is distributed to the fetal abdominal organs and lower body. [3]

Due to the greater contribution of the right ventricle to the combined ventricular output, coronary blood flow to the myocardium reflects the larger stroke volume of the right side. Blood flows to the right ventricular free wall and septum are higher compared to the left ventricle. This difference in blood flow results in greater wall thickness on the right side of the fetal heart relative to the left side. Similar to the adult heart, fetal ventricular output depends on heart rate, pulmonary artery and aortic pressures, and contractility. The relationship between mean right atrial pressure (an index of ventricular volume at the end of diastole) and stroke volume demonstrates that the fetal right atrial pressure typically resides at the break point in the ascending limb, where further pressure increases do not lead to an increase in stroke volume. Therefore, the contribution of Starling mechanisms (which regulate the heart's ability to adapt to changes in venous return) to increasing right heart output in the fetus is limited. In contrast, decreases in venous return and right atrial pressure result in a decrease in stroke volume. The left ventricle exhibits a similar relationship between atrial pressure and stroke volume, with a small amount of preload reserve remaining even near the break point. Unlike the fetal right ventricle, the left side is not sensitive to increases in aortic pressure. As a result, postnatal increases in systemic blood pressure do not reduce left ventricular stroke volume and left ventricular output increases to meet the demands of the systemic circulation. While the fetal heart has limited capacity for increasing stroke volume through Starling mechanisms, late-gestation fetal hearts possess β -adrenergic receptors comparable to those found in adults, allowing circulating catecholamines to increase contractility and potentially boost stroke volume by 50%. [3]

Throughout the second half of gestation, the fetal heart rate decreases, particularly between 20 and 30 weeks, but it still remains more than twice the resting heart rate of adults. When analysing episodes of low heart rate variability, the mean heart rate decreases from 30 weeks until term.

However, when considering all heart rate data, the mean heart rate stabilizes at around 142 beats/min during the last 10 weeks of gestation. The variability in mean heart rate over a 24-hour period shows a nadir between 2 AM and 6 AM and a peak between 8 AM and 10 AM. Most fetal heart rate accelerations coincide with limb movement, which primarily reflects central neuronal brainstem activity. Additionally, movement-related decreases in venous return and reflex tachycardia may contribute to heart rate accelerations. As ventricular stroke volumes decrease with an increase in heart rate, fetal cardiac output remains constant within a heart rate range of 120 to 180 beats/min. The primary effect of this inverse relationship between heart rate and stroke volume is a change in end-diastolic dimension. By maintaining a constant end-diastolic dimension, stroke volume does not decrease, and cardiac output increases. [3]

At birth, significant changes occur in vascular distribution upon the first breath. Alveolar expansion and the subsequent rise in alveolar capillary oxygen tension led to a substantial decrease in pulmonary microvascular resistance. This decrease in pulmonary vascular resistance has two effects. First, it causes a decrease in right atrial afterload and right atrial pressure. Second, the increased pulmonary flow augments venous return into the left atrium, resulting in elevated left atrial pressure. As a result, the left atrial pressure surpasses the right atrial pressure, leading to the closure of the foramen ovale. The highly oxygenated blood from the lungs returns to the left atrium, left ventricle, and aorta, while the decrease in pulmonary vascular resistance reduces the pressure in the pulmonary trunk, allowing oxygen-rich blood to flow back into the ductus arteriosus. This increase in oxygen tension in the ductus arteriosus triggers localized vasoconstriction, altering the ductus response to prostaglandins. Simultaneously, the clamping or spontaneous constriction of the umbilical cord ceases placental blood flow, decreases venous return, and potentially intensifies the reduction in right atrial pressure. [3]

Organ	Biventricular cardiac output (%)
Placenta	40
Brain	13
Heart	3.5
Lung	7
Liver	2.5
Gastrointestinal Tract	5
Adrenal Glands	0.5
Kidney	2.5
Spleen	1
Body	25

Table 1.1: Distribution of Cardiac Output to Fetal Organs [3]

The regulation of fetal heart rate (FHR), cardiac contractility, and vascular tone is influenced by the sympathetic and parasympathetic systems through reflex stimulation of peripheral baroreceptors, chemoreceptors, and central mechanisms. The fetal sympathetic system develops early, while the parasympathetic system develops later. However, in the third trimester, the increasing parasympathetic tone leads to a characteristic decrease in FHR with periods of reduced FHR reactivity. This decrease can be reversed by blocking the parasympathetic system with atropine, indicating its contribution. The interplay between sympathetic and parasympathetic inputs results in variability in the fetal heart rate and basal heart rate over short periods of time, even when both inputs are removed. [3]

While the presence of circulating catecholamines can maintain blood pressure in the absence of fetal sympathetic innervation, precise control of blood pressure and FHR requires an intact sympathetic system. Without functional adrenergic innervation, hypoxia-induced increases in peripheral, renal, and splanchnic bed vascular resistances and blood pressure do not occur. However, hypoxia-related changes in blood flow still affect organs like the lungs, heart, adrenal glands, and brain, indicating the involvement of local and endocrine factors in blood flow regulation. [3]

The carotid body and arch of the aorta contain receptors that respond to changes in blood pressure and respiratory gases, influencing heart rate and vascular tone. Fetal baroreflex sensitivity, which refers to the responsiveness of heart rate to changes in blood pressure, is lower compared to adults but increases significantly in late gestation. While intact baroreceptors are not necessary for establishing the set point of FHR, their absence leads to increased FHR variability. The same observation applies to fetal blood pressure, suggesting that arterial baroreceptors help stabilize blood pressure during fetal body or breathing movements. Changes in baroreceptor tone likely contribute to the observed increase in mean fetal blood pressure during late gestation. Absence of functional chemoreceptors affects resting peripheral vascular tone, and these receptors play a crucial role in fetal reflex responses to hypoxia. [3]

Adrenocorticotrophic hormone (ACTH) and catecholamines are discussed in later sections that focus on the fetal adrenal and thyroid glands. [3]

By the end of the first trimester, significant amounts of arginine vasopressin (AVP) are present in the human fetal neurohypophysis. Fetal plasma levels of AVP increase in response to changes in fetal plasma osmolality or maternal osmolality, as well as decreases in fetal intravascular volume or systemic blood pressure. AVP secretion in late-gestation fetuses, similar to adults, is regulated by osmoreceptor and volume/baroreceptor pathways. Hypoxia is a potent stimulus for fetal AVP secretion, with hypoxemia causing a significant increase in AVP levels. Fetal responsiveness to hypoxia is much greater than that of adults, and it appears to increase further in the second half of gestation. [3]

Infusion of AVP in fetuses leads to dose-dependent increases in mean blood pressure and decreases in heart rate, even at plasma levels lower than those required to produce similar effects in adults. Different receptors (V1) than those involved in AVP's antidiuretic effects in the kidneys (V2) are responsible for AVP's contributions to fetal circulatory adjustments during hemorrhage, hypotension, and hypoxia. The effects of corticotropin-releasing factor (CRF) and AVP may contribute to the increase in plasma ACTH and cortisol levels induced by hypoxia. AVP also affects blood flow in various organs, including the periphery, placenta, myocardium, and brain, aligning with the cardiovascular changes observed during acute hypoxia. Some of these responses are diminished when AVP receptors are blocked, suggesting that AVP helps facilitate oxygen availability to the fetus during hypoxic challenges. However, certain hypoxia-related responses, such as decreases in renal and pulmonary blood flow and increased adrenal blood flow, are not observed during AVP infusions. [3]

Fetal plasma renin levels are typically elevated during late gestation. Various stimuli, including changes in sodium concentration in the tubules, reductions in blood volume, vascular pressure, renal perfusion pressure, and hypoxemia, increase fetal plasma renin activity. The relationship between fetal renal perfusion pressure and plasma renin activity is similar to that of adults. Like adults, fetal renin gene expression is directly regulated by renal sympathetic nerve activity.[3]

While fetal plasma angiotensin II (All) levels increase in response to small changes in blood volume and hypoxemia, fetal All and aldosterone levels do not increase proportionally to changes in plasma renin activity. This discrepancy may be attributed to the significant contribution of the placenta to All clearance in the fetus compared to adults. Additionally, limited availability of angiotensin-converting enzyme (ACE) due to reduced pulmonary blood flow and inhibition of aldosterone secretion by high circulating atrial natriuretic factor (ANF) levels may also contribute to this uncoupling. These factors result in reduced All production, aldosterone responses to All, and feedback inhibition of renin, leading to elevated renin and reduced All and aldosterone levels during fetal life. [3]

Infusion of All in fetuses increases mean arterial blood pressure. Unlike AVP, All infusion initially causes a reflex bradycardia but subsequently increases heart rate through direct effects on the heart and reduced baroreflex responsiveness. Both AVP and All increase fetal blood pressure to levels comparable to those seen during hypoxemia. However, All does not reduce peripheral blood flow, possibly due to the already maximum response of muscle, skin, and bone circulation to All, which limits further increases in resting tone. All infusions decrease renal blood flow and increase umbilical vascular resistance, but they do not affect absolute placental blood flow. The human fetal kidney only contains the AT₂ subtype of All receptors, which differs from the AT₁ subtype found in the adult kidney. These maturational differences in receptor subtypes correspond to earlier studies that identified distinct All effects on fetal renal and peripheral vascular beds, indicating that the receptors mediating All responses in these beds differ during fetal life. [3]

1.3.1 Electrical activity of the heart

In the fully developed adult heart, the maintenance of electrical impulse generation is orchestrated by specialized cells within the cardiac conduction system. This intricate system encompasses several components, including the sinoatrial (SA) node, atrioventricular (AV) node, atrioventricular bundle (bundle of His), atrioventricular bundle branches, and Purkinje cells [4].

The SA node, situated in the right atrium near the superior vena cava, serves as the primary pacemaker of the heart. It possesses the highest inherent rate of depolarization and serves as the

initiator of the sinus rhythm, the heart's normal electrical pattern preceding contraction. The impulse generated in the SA node propagates through the atria via internodal pathways and subsequently reaches the AV node [4].

Located in the inferior portion of the right atrium within the atrioventricular septum, the AV node acts as a secondary pacemaker. It receives the impulse from the atria but introduces a crucial delay before transmitting it to the atrioventricular bundle. This delay allows the atrial cardiomyocytes to complete their contraction before the impulse is conveyed to the ventricles [4].

From the AV node, the impulse travels through the atrioventricular bundle (bundle of His) and further divides into the left and right bundle branches. The left bundle branch supplies the left ventricle, while the right bundle branch supplies the right ventricle. These bundle branches extend to the apex of the heart and interface with the Purkinje fibers [4].

The Purkinje fibers constitute additional specialized conducting fibers responsible for the rapid transmission of the impulse to the ventricular myocardial cells. They traverse throughout the myocardium, originating from the apex and extending toward the atrioventricular septum and the base of the heart. Consequently, the electrical impulse reaches all ventricular muscle cells within approximately 75 ms, initiating ventricular contraction from the apex and propagating towards the base of the heart [4].

The entire process, from the initiation of the impulse in the SA node to the depolarization of the ventricles, spans approximately 225 ms.

Moreover, the cardiac action potential, a transient and reversible wavefront of electromagnetochemical activity responsible for initiating the cardiac impulse, involves a complex series of transmembrane ion movements, resulting in a net flow of electric current across the cell membrane. The cell membrane contains ion channels that open under specific conditions, allowing charged ions such as sodium, potassium, and calcium to pass through. The distribution of these charged ions across the cell membrane is maintained by energy-expending membrane ion pumps and ion exchange complexes [5].

At rest, a typical cardiac cell maintains a negative electrical potential within its interior relative to the extracellular space, a phenomenon largely governed by the ATPase pump, which maintains higher intracellular potassium ion concentrations and lower sodium ion concentrations. Depolarization occurs when the resting potential becomes less negative, either spontaneously (as in nodes like the

SA or AV node) or due to the arrival of an electrical current (as in cells like Purkinje cells or cardiac myocytes). This depolarization point is known as the activation threshold and initiates phase 0 of the action potential. Phase 0 is characterized by rapid depolarization, raising the cell's potential close to +20 to 30 mV. The rate of rise of phase 0, termed $\dot{V}_{\max}$, is a critical determinant of conduction velocity in the heart. Following phase 0, there is often a brief, rapid repolarization phase (phase 1), causing a notch in the action potential. The plateau phase (phase 2) of the action potential is sustained by inward calcium currents, while phase 3 repolarization is primarily driven by outward potassium currents [5].

Furthermore, spontaneous automaticity, primarily observed in pacemaker cells of the sinoatrial node, involves a gradual depolarization of the cell membrane during phase 4 of the action potential, eventually reaching the activation or threshold potential. Subsidiary pacemakers in atrial, AV junctional cells, and His-Purkinje cells can also exhibit spontaneous depolarization but at slower rates than the sinoatrial node. Spontaneous automaticity may arise due to various factors, including changes in ion currents and concentrations [5].

Throughout development, the morphology of the action potential and the corresponding physiology of ion currents undergo changes:

- Resting Membrane Potential: As development progresses, an increase in sodium-potassium ATPase activity, potentially driven by the expression of different sodium-potassium ATPase pump isoforms, contributes to a more negative resting membrane potential. Additionally, an increase in membrane permeability to potassium also contributes to the observed more negative resting potential [5].
- Action Potential Upstroke, Phase 0: With maturation, there are documented increases in the amplitude and $\dot{V}_{\max}$ of action potential phase 0. While some of these changes relate to the increased resting membrane potential, it appears that developmental changes in the structure or function of the ion channel responsible for the action potential upstroke also play a role [5].
- Action Potential Phase 1: The development of the spike-and-dome appearance in Phase 1 correlates with the expression of certain genes associated with the transient outward current I_{to} , such as KCNIP2 and KCND3. This maturation of the transient outward current is also associated with the phenomenon of "cardiac memory," referring to changes in repolarization persisting after chronic pacing [5].
- Action Potential Plateau and Repolarization, Phases 2 and 3: The slow inward calcium current (I_{Ca-L}) significantly contributes to the action potential plateau. During development, shifts occur in the

relative contributions of L-type and T-type calcium channels, affecting the calcium transient. In rabbit studies, progressive increases in myocardial calcium current density and kinetics have been observed from fetal to adult life, impacting excitation-contraction coupling and cardiac function [5].

- Impulse Formation (Phase 4) and Intra-Atrial and Atrioventricular Conduction: The mechanisms governing pacemaker formation during development are not fully understood, but factors such as physical contact between myocardial cells and non-myocardial elements may influence pacemaker cell induction. Additionally, looping of the heart and the influence of signaling molecules like endothelin 1 and neural crest cells play important roles in inducing cardiomyogenic precursor cells to differentiate into specialized cells of the cardiac conduction system [5].

- Intra-atrial conduction tends to follow specific directions roughly aligned with the anatomic courses of putative internodal pathways. Electrophysiologic differences in atrial action potential morphology and intra-atrial conduction have been observed during development, with neonatal atrial action potential durations typically shorter and more uniform compared to adults [5].

- In the human heart, the AV node and specialized conduction system develop after the heart's looping process is completed, usually around 25 days of gestation. The transcriptional regulation of cardiomyogenic precursor cells into specialized conduction system cells involves factors like GATA6, Nkx2-5, Tbx2, Tbx3, Tbx5, and homeodomain-only protein. Immunohistochemical studies in humans have revealed that the entire AV conduction system develops from a single ring of specialized tissue surrounding the interventricular foramen [5].

- The physiology of atrioventricular conduction in the neonatal heart is not fully understood, and the AV node can be functionally and histologically subdivided into different regions. The refractory period of the AV conduction system in neonates is longer than the ventricular refractory period. Normal fetal AV conduction intervals have been observed through clinical techniques like fetal echocardiography and magnetocardiography at specific gestational ages [5].

1.3.2 Normal and Abnormalities of FHR

The myocardium, or heart muscle, begins rhythmic contractions around 3 weeks after conception due to the activity of spontaneously depolarizing myocardial pacemaker cells in the developing heart. The maturation of the myocardium continues even after birth. While the precise timing of the atrioventricular (AV) electromechanical relationship onset in humans is not known, by approximately 6 weeks post-conception, AV synchrony can be observed using standard Doppler techniques. At around 5-6 weeks, the normal average fetal heart rate is about 110 beats per minute (bpm). [6]

As the conduction system of the heart further matures, including the identification of the sinoatrial (SA) node as the primary pacemaker with the highest intrinsic rate of spontaneous depolarization, the heart rate increases to around 170 bpm by 9-10 weeks. Subsequently, the heart rate decreases to approximately 150 bpm by 14 weeks, possibly due to increasing parasympathetic control and improved myocardial contractility. Around 20 weeks, the average fetal heart rate is 140 bpm, with a standard deviation of 20 bpm. There is a gradual decrease in heart rate to around 130 bpm by term.

In a healthy fetus, the heart rate remains regular and typically falls within the range of 110 to 180 bpm. There is a beat-to-beat variation of 5-15 bpm. These heart rate variations are considered normal in a healthy fetal heart. [6]

Fetal rhythm abnormalities, including irregular, fast, or slow fetal heart rates, occur in up to 2% of pregnancies and account for 10-20% of referrals to fetal cardiologists. Obstetrical clinicians usually detect these abnormalities using a Doppler device during routine assessments of pregnant mothers. While such assessments begin around 12-14 weeks, most fetal arrhythmias are detected after 20 weeks of gestation. Most affected pregnancies involve isolated premature atrial contractions (PACs), which may resolve spontaneously. Less than 10% of referrals for fetal rhythm abnormalities have sustained tachyarrhythmias or bradyarrhythmias that are considered clinically significant and may indicate systemic disease or compromise fetal circulation. [6]

PACs are commonly identified in third-trimester fetuses, and their frequency can vary. They may be conducted or blocked at the atrioventricular (AV) node. In cases of atrial bigeminy, where the PACs occur every other beat, Doppler devices may not detect the Doppler signal of the ventricular output following the extrasystole. These pregnancies are often referred due to intermittent or persistent fetal bradycardia. While isolated PACs are usually benign and resolve before or shortly after birth, about 1-3% of affected fetuses experience intermittent runs of supraventricular tachycardia (SVT), which can be problematic. Fetal PACs detected along with cardiomegaly, ventricular systolic dysfunction, AV

valve regurgitation, or hydrops may indicate the possibility of SVT. In such cases, regular obstetrical ultrasound assessments are warranted until the arrhythmia resolves or until delivery. Less than 10% of affected fetuses have associated structural heart disease, including significant tricuspid or mitral insufficiency, atrial dilation, intracardiac tumors, etc. These fetal heart abnormalities may not tolerate the minor hemodynamic alterations caused by the extrasystoles. [6]

Premature ventricular contractions (PVCs) in fetuses are rare. When detected, further evaluation is necessary to exclude myocardial disease, intracardiac tumors, and any evidence of cardiovascular compromise. Serial prenatal assessments and postnatal evaluations are essential to confirm the nature of the ectopy and exclude intermittent runs of more serious tachyarrhythmias. [6]

Fetal tachycardia is diagnosed when the ventricular rate exceeds 180 bpm. Most tachyarrhythmias diagnosed after birth are also detected prenatally. The majority of fetal tachycardias are of supraventricular origin, with supraventricular tachycardia (SVT) associated with an atrioventricular (AV) accessory pathway being the most common. SVTs can be categorized based on the ventricular-atrial (V-A) interval, distinguishing short V-A interval SVTs, long V-A interval SVTs, those with superimposed V and A waves, and atrial re-entrant tachycardias. The mechanism of the SVT plays a crucial role in determining the most appropriate management strategy. Fetal SVT caused by an accessory AV pathway is typically associated with ventricular rates of 230-280 bpm and a shorter V-A interval relative to the A-V interval (known as short V-A tachycardia) with 1:1 atrioventricular conduction. At birth, about 10% of affected fetuses have Wolff-Parkinson-White syndrome. Long V-A tachycardias, where the A-V interval is shorter than the V-A interval, include sinus tachycardia, ectopic atrial tachycardia (EAT), and permanent junctional reciprocating tachycardia (PJRT). Differences in timing, nature of onset and offset, and beat-to-beat variability can help differentiate between these forms of long V-A SVTs. Fetal atrial flutter is usually identified late in gestation, characterized by atrial rates ranging from 300-550 bpm and variable A-V conduction and ventricular rates. [6]

Hydrops fetalis, a severe manifestation of fetal heart failure, is observed in about 40-50% of fetuses with SVT. SVT reduces diastolic filling time, combined with impaired relaxation and reduced compliance of the fetal myocardium, resulting in increased atrial and central venous pressures. This leads to blood flow reversal in the systemic and pulmonary veins during atrial systole, indicating elevated hydrostatic pressure and plasma protein extravasation into the interstitial space. The increased central venous pressure can breach the ductus venosus, impairing umbilical venous flow and leading to placental edema, dysfunction, and fetal hypoxemia. [6]

Management strategies have evolved over the past two decades to treat fetal SVT, primarily in cases of heart failure or high risk. Treatment often involves maternal/transplacental administration of antiarrhythmic medications. However, the pharmacokinetic changes during pregnancy, altered distribution of drugs in the maternal-fetal-placental compartments, and the impact of fetal and placental hydrops on drug distribution require careful consideration. Various antiarrhythmic medications have been used, including digoxin, propranolol, flecainide, sotalol, propafenone, verapamil, and amiodarone. The choice of medication depends on the specific SVT mechanism and the presence or absence of hydrops. [6]

In cases of hydrops fetalis, where severe fetal heart failure is present, a combination of medications is often required, and the treatment duration may be longer. Some medical teams opt to initiate stronger antiarrhythmic therapy alongside digoxin to achieve faster success and reduce the risk of mortality and morbidity associated with significant fetal SVT. [6]

Fetal bradycardia is diagnosed when the ventricular rate is below 110 bpm. The most common cause of fetal bradycardia is sinus bradycardia, which can occur due to vagal stimulation during ultrasound examinations, fetal distress, or systemic disease. Fetal bradycardia with a prompt return to a normal heart rate is often observed during ultrasound examinations and indicates that the fetus has reasonable reserve. Sinus bradycardia can rarely be a sign of long QT syndrome. Intermittent 2:1 AV block without alterations in atrioventricular conduction can also aid in making this diagnosis. [6]

Fetal AV block is another cause of bradycardia, most commonly presenting as complete AV block but occasionally as second-degree or even first-degree AV block, as diagnosed with A-V intervals and magnetocardiography. Maternal autoantibodies are associated with approximately 45-48% of cases of fetal AV block, while structural heart disease accounts for another 45-48% of cases. Isolated AV block with or without myocardial disease is typically caused by the transplacental passage of maternal autoantibodies, such as anti-SSA/Ro and/or anti-SSB/La. The deposition of these antibodies along the conduction system and myocardium leads to inflammatory reactions and fibrosis, affecting the AV node and endocardium. While these antibodies can be found in women with autoimmune diseases, most mothers of affected fetuses do not have clinical autoimmune disease at the time of AV block diagnosis. [6]

Maternal autoantibody-mediated AV block is an acquired condition during pregnancy that likely requires specific predisposing factors in the fetus or external factors such as infection. Approximately 15-20% of fetuses with autoimmune-mediated AV block also have more diffuse myocardial disease,

which can lead to endocardial fibrosis and ventricular dysfunction. The presence of myocardial disease and ventricular rates below 50 bpm are important risk factors for mortality. Maternal administration of corticosteroids, particularly fluorinated glucocorticoids like dexamethasone, has been used in treating this condition due to its anti-inflammatory properties. Rare cases have shown a reversal in the severity of heart block with corticosteroid treatment. Maternal and neonatal plasmapheresis have varying efficacy in this disease. Fetal ventricular pacing has been attempted but with limited success, likely due to the absence of AV synchrony in the presence of severe myocardial dysfunction. Intravenous γ -globulin, administered to the mother or directly to the fetus through cordocentesis, has been suggested as a potential treatment for fetuses and neonates with reduced myocardial function indicating more diffuse disease. Maternal administration of β -sympathomimetics is also used, especially in pregnancies with low fetal ventricular rates or evidence of myocardial disease, to support cardiac function and improve ventricular rate. [6]

With close surveillance, the use of corticosteroids, delivery at 35-37 weeks or earlier in the presence of fetal distress or cardiovascular compromise, aggressive neonatal cardiac intensive care management, and early permanent pacemaker therapy, the mortality rate for prenatally diagnosed autoimmune-mediated AV block has significantly decreased. [6]

1.4 Fetal Hypoxia

During fetal development, the oxygen environment and the need for efficient gas exchange differ significantly from that in adults. Sir Joseph Barcroft, in 1946, likened this situation to an "in utero Mount Everest expedition," highlighting the analogy between fetal oxygen levels and high-altitude conditions. However, this doesn't mean the fetus lacks oxygenation during gestation. Fetal physiology employs various adaptive mechanisms, similar to those seen in high-altitude acclimatization, ensuring adequate oxygen consumption. Factors like high blood flow, efficient placental gas exchange, and hematologic adaptations, including increased fetal hemoglobin, contribute to fetal oxygenation. Additionally, the fetal brain has a lower metabolic rate, reducing oxygen demands. [7]

Precise regulation of the fetal heart rate (FHR) is crucial for maintaining oxygenation. The fetus encounters periods of reduced oxygen supply during labor, known as hypoxic episodes. In response, the FHR decelerates, reducing myocardial workload and oxygen requirements, considered a protective mechanism. Concurrently, fetal blood pressure increases due to peripheral vasoconstriction, redirecting blood to vital organs and allowing aerobic metabolism. Stress hormones further enhance these adaptations. The fetus also has an increased anaerobic capacity and can reduce metabolic activity, enhancing oxygen diffusion during hypoxia. [7]

During labor, there's a temporary decrease in pH and oxygen tension, along with increased carbon dioxide concentration, leading to respiratory acidosis. However, this resolves after birth with the first breaths and doesn't cause neonatal complications. Overall, these mechanisms ensure fetal oxygenation despite variations in the intrauterine environment [7].

Fetal hypoxia and intrauterine hypoxia are intricately linked, as both entail a reduction in the supply of oxygen to the developing fetus during its residence in the uterus. The fetus relies on the mother for the exchange of oxygen and carbon dioxide through the placenta, contingent on the presence of adequate maternal blood gas concentrations, uterine blood supply, placental transfer, and fetal gas transport. Disruption of any of these factors can lead to fetal hypoxia, potentially culminating in acidosis. Severe and prolonged episodes of hypoxia and acidosis are associated with significant morbidity and mortality, with the potential for enduring effects on the child [8].

Intrauterine hypoxia is associated with a variety of maternal, placental, and fetal conditions, each of which may manifest differently and yield diverse outcomes. It can be categorized into three subtypes: pre-placental hypoxia (affecting both the mother and the fetus), utero-placental hypoxia (involving

the circulation within the utero-placental region), and post-placental hypoxia (where only the fetus experiences hypoxia). Our focus here will be on the first two subtypes, as post-placental hypoxia is predominantly linked to fetal diseases rather than the direct consequences of hypoxia on the fetus [8].

Pre-placental hypoxia can stem from a hypoxic environment, such as residing at high altitudes, and pre-existing maternal cardiovascular conditions. Maternal factors like anemia, infections, and chronic inflammation can further impede maternal oxygen uptake and the delivery of oxygen to the fetus, thereby increasing the risk of adverse pregnancy outcomes [8].

Utero-placental hypoxia is connected to irregular placental implantation early in gestation and vascular disorders within the placenta later in pregnancy. One common manifestation of utero-placental hypoxia is pre-eclampsia, characterized by hypertension and proteinuria. This condition can lead to intrauterine hypoxia and oxidative stress in the fetus, resulting in intrauterine growth restriction (IUGR) and premature birth [8].

CHAPTER 2: CARDIOTOCOGRAPHY

The cardiotocograph (CTG) is a continuous electronic record of the fetal heart rate, obtained via an ultrasound transducer placed on the mother's abdomen (external or indirect CTG). Simultaneously, a second transducer placed over the uterine fundus records any uterine activity. Both fetal heart rate and uterine activity are traced simultaneously onto a paper strip. The CTG allows assessment of various components of the fetal heart rate, including the baseline rate, baseline variability, accelerations, and decelerations. The relationship between fetal heart rate and the timing of uterine contractions is also examined.[9]

Cardiotocography is widely used in maternity care during both the antepartum and intrapartum periods. This review focuses on the application of CTG during pregnancy and before labor begins. It is important to note that there is a separate Cochrane review that evaluates the effectiveness of continuous intrapartum cardiotocography. [9]

The term "electronic fetal monitoring" is sometimes used interchangeably with CTG monitoring. However, it is considered a less precise term because CTG monitoring not only includes monitoring the fetal heart rate but also the mother's contractions. Additionally, other forms of fetal monitoring, such as ECG and fetal pulse oximetry, might also fall under the category of "electronic" monitoring. [9]

Antenatal CTG is a commonly used method for assessing fetal well-being during pregnancy. It may be used independently, known as the "non-stress test," or in conjunction with the stimulation of uterine activity to observe the fetal heart rate response, referred to as the "contraction stress test." [9]

The fetal heart rate (FHR) is recorded and displayed on both the CTG paper and the CTG monitor. Additionally, it is audibly detected, with the option to adjust the volume as needed.

To measure the FHR, a Doppler ultrasound device is utilized, which involves transmitting a sound wave through the mother's abdomen. The speed of sound in a medium is influenced by its density, with water conducting sound approximately four times faster than air. [9]

When the sound wave encounters an interface between substances with different densities, part of the sound passes through the second substance, while some is reflected towards the source. The Doppler ultrasound transducer detects this reflected sound wave. [9]

To achieve a good signal, the Doppler ultrasound apparatus is positioned on the maternal abdomen over the fetus's anterior shoulder. A water-based ultrasonic gel is applied between the transducer and the abdomen to ensure proper contact, minimizing interference. (Figure 2.1) [9]

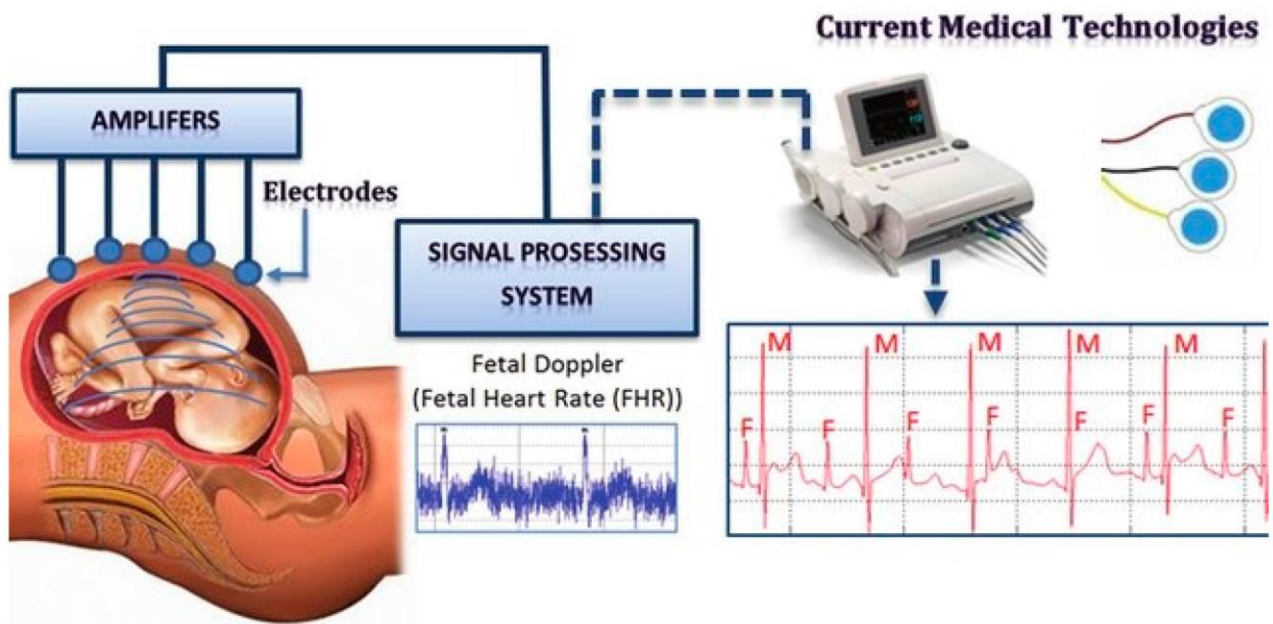
The transducer functions to produce and receive sound waves. It generates sound by passing a high-frequency electrical current through a piezoelectric crystal, causing the crystal to change shape and produce sound waves that propagate through the woman's abdomen. The piezoelectric effect also allows the crystal to convert some of the energy from reflected sound waves into an electric current, which is used to determine the FHR. [9]

The frequency of the sound waves is determined by how often the electrical current to the piezoelectric crystal is turned on and off, measured in Hertz (cycles per second) (Hz).

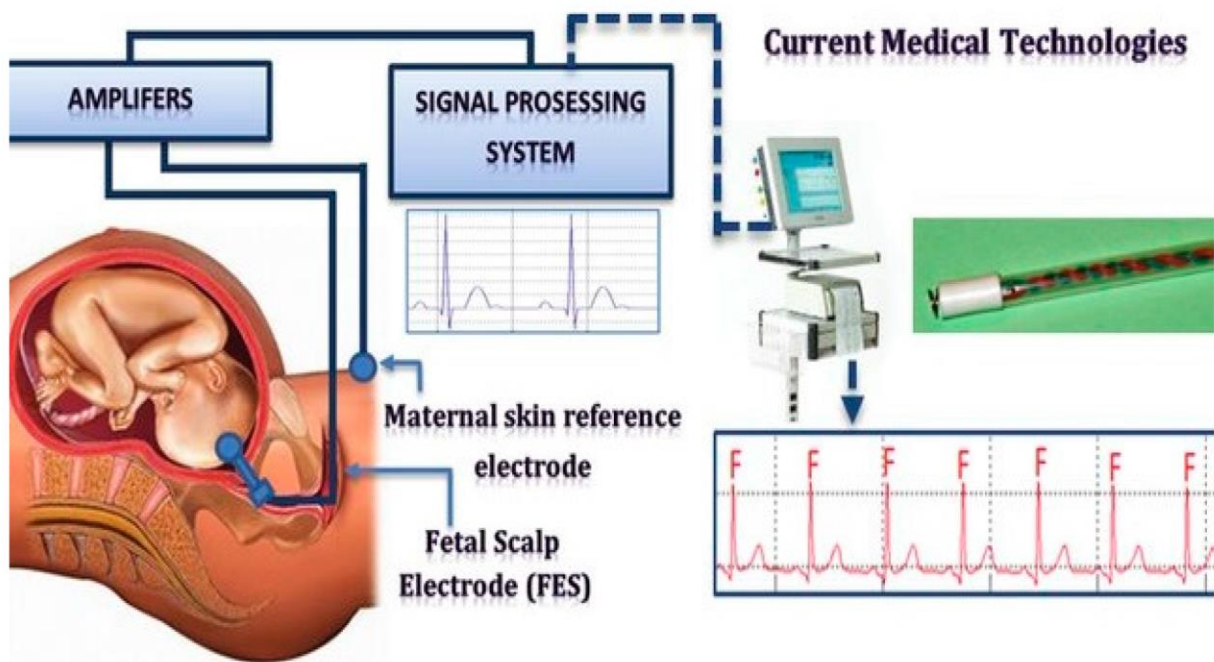
It is important to note that in this context, Doppler ultrasound is not utilized to create an image of the fetus but rather to assess the frequency changes of the Doppler shift within the fetal circulation. [9].

Another method of fetal monitoring involves an invasive approach where an electrode is affixed to the baby's head. To use this method effectively, the membranes should have already ruptured or must be intentionally ruptured to enable the application of the scalp clip. Furthermore, there should be adequate dilation of the cervix to allow for the passage of the electrode. (Figure 2.1) [9]

In summary, this invasive technique offers an alternative means of monitoring the fetal heart rate, but it necessitates certain conditions for its appropriateness, including membrane status and cervical dilation. It is essential for healthcare providers to carefully assess these factors before employing this method of fetal monitoring during pregnancy and labor. [9]



(a)



(b)

Figure 2.1: external CTG (on top/ a)) and internal CTG (bottom/ b))

To measure uterine activity, an abdominal transducer known as the 'toco' is utilized. This toco is placed on the maternal anterior abdominal wall over the uterus's fundus and secured with a stretchy elastic band. Its purpose is to monitor the frequency and duration of uterine contractions. The amplitude of the tocograph is influenced by changes in the shape and tone of the anterior abdominal wall, rather than directly reflecting the strength of the uterine contractions. When the uterus contracts, it alters

the shape and tone of the overlying abdominal wall, generating a pressure wave that is captured by the tocograph. (Figure 2.2) [9]

It is important to note that while the tocograph records the pressure changes in the abdominal wall, other factors such as vomiting or the valsalva maneuver can also affect the abdominal wall's shape and tone, leading to a potential misrepresentation of uterine activity on the tocograph. [9]

Assessing the strength of contractions is best accomplished by considering the woman's level of pain, whether there is progress in labor, and the presence of ongoing changes (decelerations) on the CTG trace. Fewer contractions with adequate strength and duration may be more effective in achieving progress during labor compared to frequent, weak, and short-lived contractions. (Figure 2.3) [9]



Figure 2.2: tocograph machine

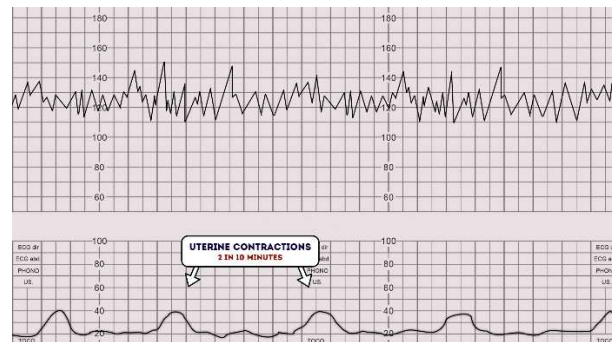


Figure 2.3: Uterine contractions' signal

Alternatively, there is a method involving direct manometry or a pressure transducer on the tip of a flexible catheter, which is inserted into the uterine cavity through the cervix. This method theoretically offers more precise measurement of contraction strength and timing, including the 'resting tone.' However, it is seldom used outside of research settings in the United Kingdom due to several drawbacks. One concern is that the fetal parts create multiple compartments within the uterine cavity, causing variations in pressure across these compartments and potentially yielding inaccurate results. (Figure 2.4) [9]



Figure 2.4: Manometry machine

Proper documentation is crucial for all CTG traces, and they should be labelled with unique patient identifiers, correct time, and date, just like any other medical record. Ensuring the correct orientation of the paper is essential to accurately interpret the traces. [9]

One should also be aware of the 'paper speed,' which determines how fast the CTG trace moves. In the United Kingdom, the paper speed is 1 cm/min, while in the United States, it is 3 cm/min. Scandinavian countries use a paper speed of 2 cm. [9]

➤ Paper Printout:

Advantages: The paper printout can be conveniently inserted into the patient's hand-held notes and easily transported between different centres along with the mother. This facilitates comparisons between current and previous CTG traces for a comprehensive evaluation. [9]

Disadvantages: Paper traces are recorded on 'thermosensitive' paper, which degrades over time. To prevent fading when exposed to light, the traces are stored in dark-brown envelopes. To address this issue for risk management purposes, photocopying the CTG traces is recommended. This not only avoids fading but also enables long-term storage of the traces. [9]

➤ Electronic Display and Storage:

Electronic display offers several advantages in CTG monitoring. It allows the CTG to be shown both in the room and on a central monitor. This enables labour ward coordinators or obstetricians to monitor multiple women's CTG traces simultaneously without needing to enter each room or disturb women

in labour. Moreover, electronic storage allows the traces to be stored centrally for an extended period, ensuring easy access for review and analysis. [9]

In conclusion, proper identification, and documentation of CTG traces are essential for accurate fetal monitoring during pregnancy and labour. Both paper printouts and electronic displays have their advantages and disadvantages, but electronic storage offers greater convenience and accessibility. By utilizing the appropriate method and ensuring comprehensive recording, healthcare providers can improve the quality of care and contribute to better outcomes for mothers and their babies. [9]

2.1 Classification of Traces

Accurate interpretation of the cardiotocograph (CTG) requires a comprehensive understanding of its fundamental features, including the baseline heart rate (BHR), variability, accelerations, and decelerations. It is essential to note that the knowledge of these features and the interpretation of CTG in the antenatal period are primarily derived from its use during labour.

➤ Baseline Heart Rate [10,11]:

The baseline heart rate (BHR) indicates the average fetal heart rate over a 5–10-min period, excluding accelerations and decelerations, and is measured in beats per minute. A BHR between 110 and 160 bpm is considered normal, while a BHR below 110 bpm is termed baseline bradycardia, and above 160 bpm is termed baseline tachycardia. (Figure 2.5)

Gestational age plays a significant role in determining the BHR. As the fetus matures, there is a progressive decrease in the baseline heart rate across gestation, especially evident before 28 weeks. This decrease is thought to be influenced by the maturation of the parasympathetic system.

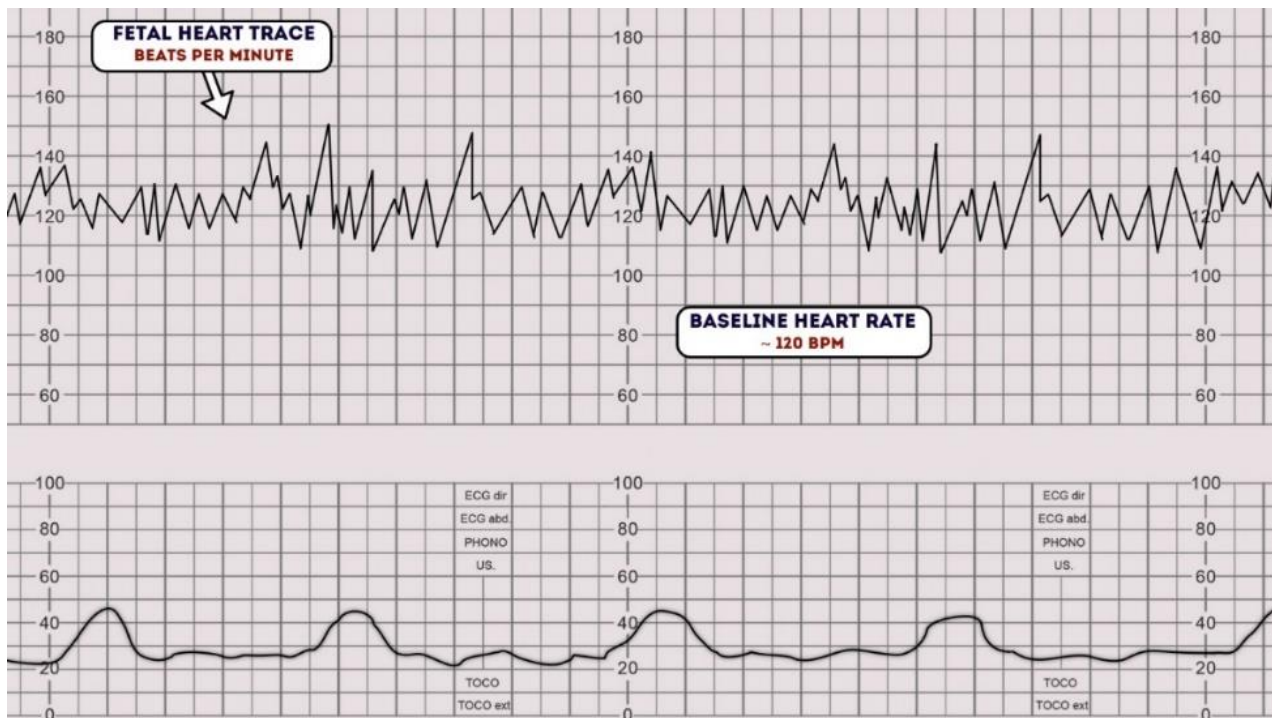


Figure 2.5: BHR signal

Uncomplicated moderate bradycardia (BHR between 100 and 109 bpm) and moderate tachycardia (BHR between 160 and 179 bpm), especially in the absence of other CTG abnormalities, do not strongly indicate adverse neonatal outcomes and have limited predictive value for fetal acidemia.

➤ Variability [10,11]:

Fetal heart rate (FHR) displays constant variation around the baseline, indicating a healthy nervous system influenced by chemoreceptors, baroreceptors, and cardiac responsiveness (Figure 2.6). Prematurity may lead to reduced variability, resulting in minimal rate fluctuation before 28 weeks. However, after 32 weeks, variability should be within the normal range. Conditions like fetal hypoxia, congenital heart anomalies, and fetal tachycardia can also cause decreased variability. Beat-to-beat or short-term variability manifests as oscillations around the baseline of 5 to 10 bpm. In contrast, long-term variability involves slower oscillations with a frequency of 3 to 10 Hz and an amplitude of 10 to 25 bpm. Loss of beat-to-beat variability is more significant than long-term variability loss and may carry ominous implications (Figure 2.7). When decreased or absent variability is observed, confirmation through fetal scalp electrode monitoring is advisable when feasible.

Interpreting FHR variability externally appears to be more reliable with second-generation fetal monitors compared to first-generation ones. Simple loss of variability may be uncomplicated, possibly due to fetal quiescence (rest-activity cycle or behaviour state), and usually resolves within 30 to

40min. Additionally, certain central nervous system depressants and medications may cause temporary loss of variability. However, it is important to differentiate between uncomplicated loss and instances indicating increased risk of acidosis or low Apgar scores.

Increased variability occurs when oscillations exceed 25 bpm, termed a saltatory pattern, often seen during the second stage of labor. This pattern may indicate acute hypoxia or mechanical compression of the umbilical cord. While no reassuring, it does not necessarily warrant immediate delivery.

FHR variability reflects the continuous balance between sympathetic and parasympathetic influences on the cardiac pacemaker. Several factors, including gestational age, baseline FHR, hypoxia, fetal sleep cycles, and maternal medication administration, influence FHR variability. Although reduced variability can be concerning, it may not always indicate a severe condition. Proper assessment of physiological and pathological factors leading to reduced CTG variability is crucial for accurate risk stratification.

While reduced variability can be an ominous sign predicting fetal compromise or death, it may present without other pathological features on the CTG trace. Therefore, careful evaluation of the underlying conditions causing reduced variability is essential for appropriate risk assessment for the fetus.

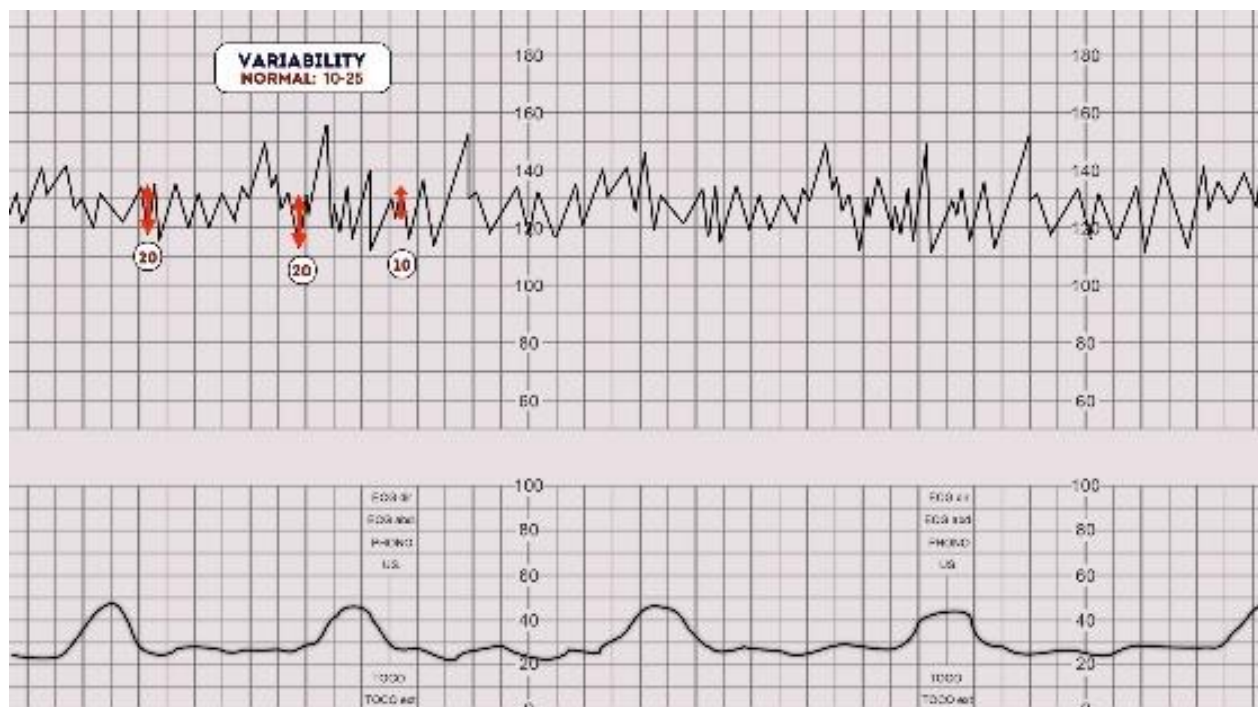


Figure 2.6: Normal Variability Signal



Figure 2.7 Reduced Variability Signal

➤ Accelerations [10,11]:

Accelerations are characterized by a sudden rise in the baseline fetal heart rate (FHR) of more than 15 bpm, persisting for over 15 s. Typically, they are regarded as a dependable sign of a healthy fetus. However, it is worth noting that the amplitude of accelerations may be lower in pregnancies before 30 weeks of gestation (Figure 2.8).

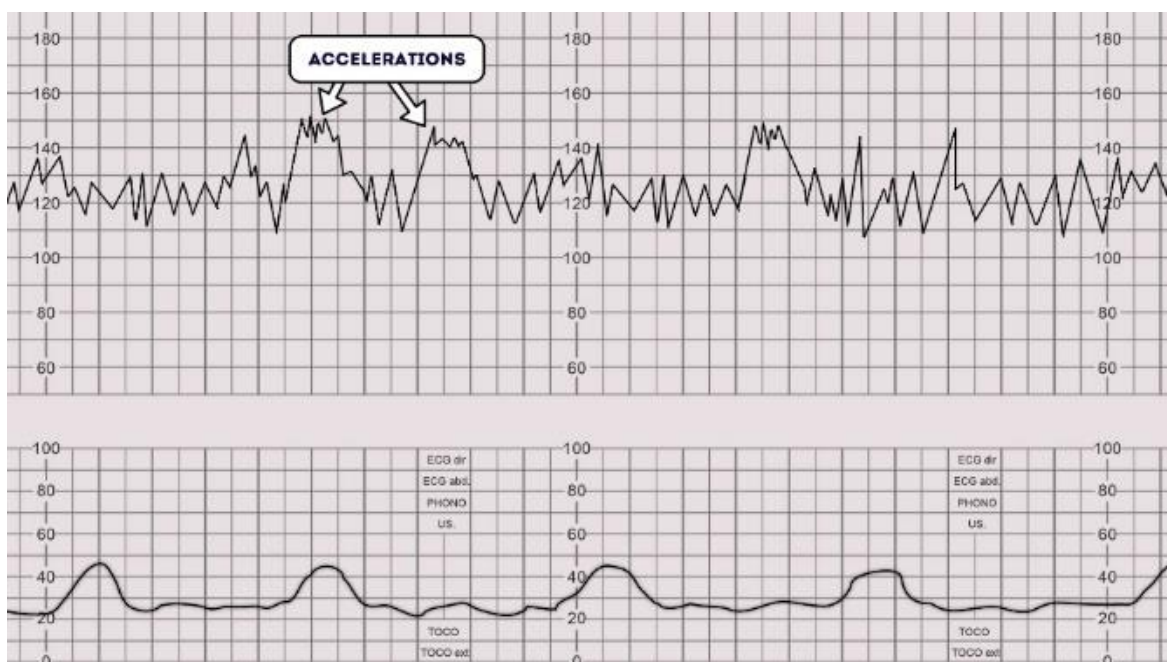


Figure 2.8: Accelerations Signal

➤ Decelerations [10,11]

- Early Decelerations:

Early decelerations are triggered by fetal head compression during uterine contractions, leading to vagal stimulation and a temporary decrease in the heart rate. These decelerations exhibit a uniform shape, with a gradual onset coinciding with the beginning of the contraction and a gradual return to the baseline coinciding with the end of the contraction. This pattern creates a mirror image of the contraction (Figure 2.9). Although early decelerations are reassuring and not associated with fetal distress, it is crucial to distinguish them carefully from other non-reassuring decelerations.

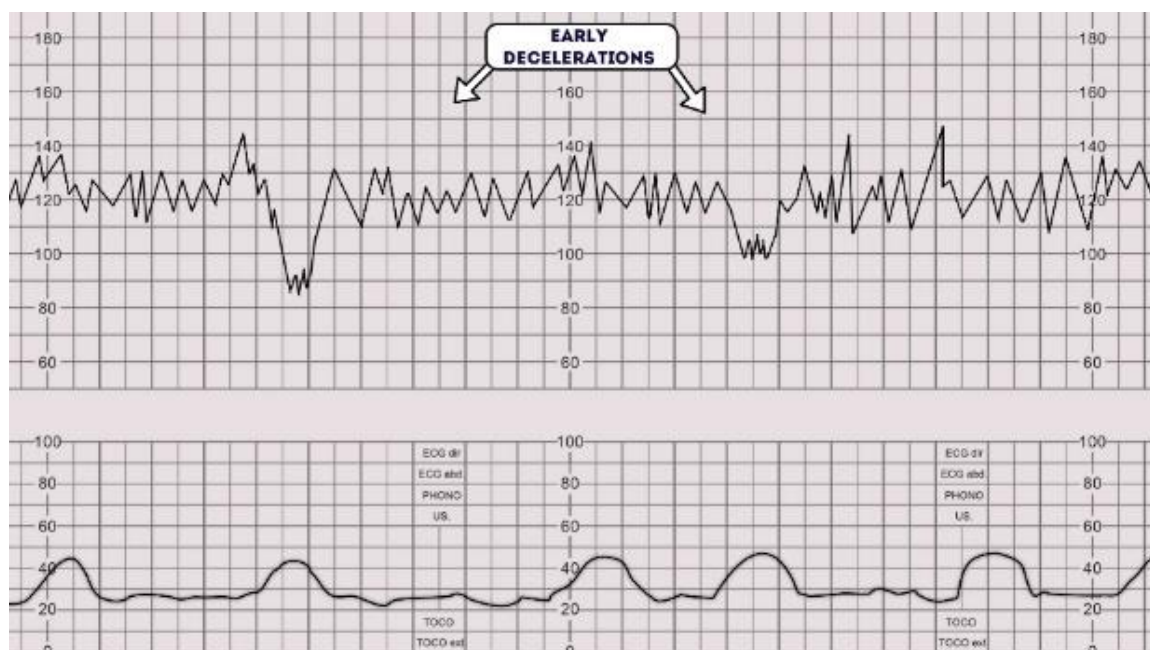


Figure 2.9: Early Deceleration Signal

- Late Decelerations:

Late decelerations are linked to uteroplacental insufficiency and are provoked by uterine contractions. Any decrease in uterine blood flow or placental dysfunction can lead to late decelerations. Conditions like maternal hypotension, uterine hyperstimulation, postdate gestation, preeclampsia, chronic hypertension, and diabetes mellitus are among the causes of placental dysfunction. Late decelerations exhibit a symmetrical decline in the fetal heart rate, commencing at or after the peak of the uterine contraction and returning to the baseline only after the contraction has ended (Figure 2.10). The descent and return are gradual and smooth. Regardless of the depth of the deceleration, all late decelerations are considered potentially concerning. A pattern of persistent late decelerations is not reassuring, and further

assessment of the fetal pH is warranted. If persistent late decelerations are associated with reduced beat-to-beat variability, it is a particularly ominous pattern.

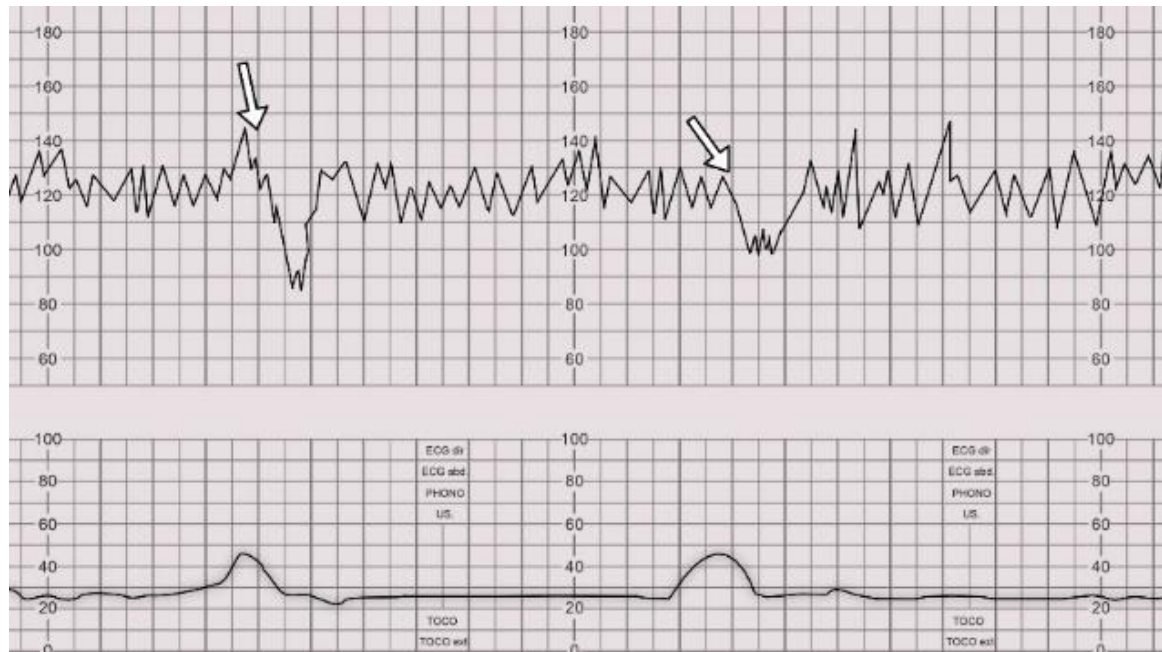


Figure 2.10: Late Decelerations Signal

- Variable Decelerations:

Variable decelerations manifest as a sharp and sudden fall in the fetal heart rate with a variable recovery phase. They are characterized by varying duration, intensity, and timing and may resemble the letters "U," "V," or "W" (Figure 2.11). These decelerations do not have a constant relationship with uterine contractions and are commonly observed during labor, especially in cases of premature rupture of membranes or decreased amniotic fluid volume. Variable decelerations are caused by compression of the umbilical cord. Initially, the umbilical vein is occluded, resulting in an acceleration (the shoulder of the deceleration), indicating a healthy response. Subsequently, occlusion of the umbilical artery leads to the sharp downward slope. Finally, the recovery phase occurs as the compression is relieved, resulting in a sharp return to the baseline, which may be followed by another brief healthy acceleration or shoulder.

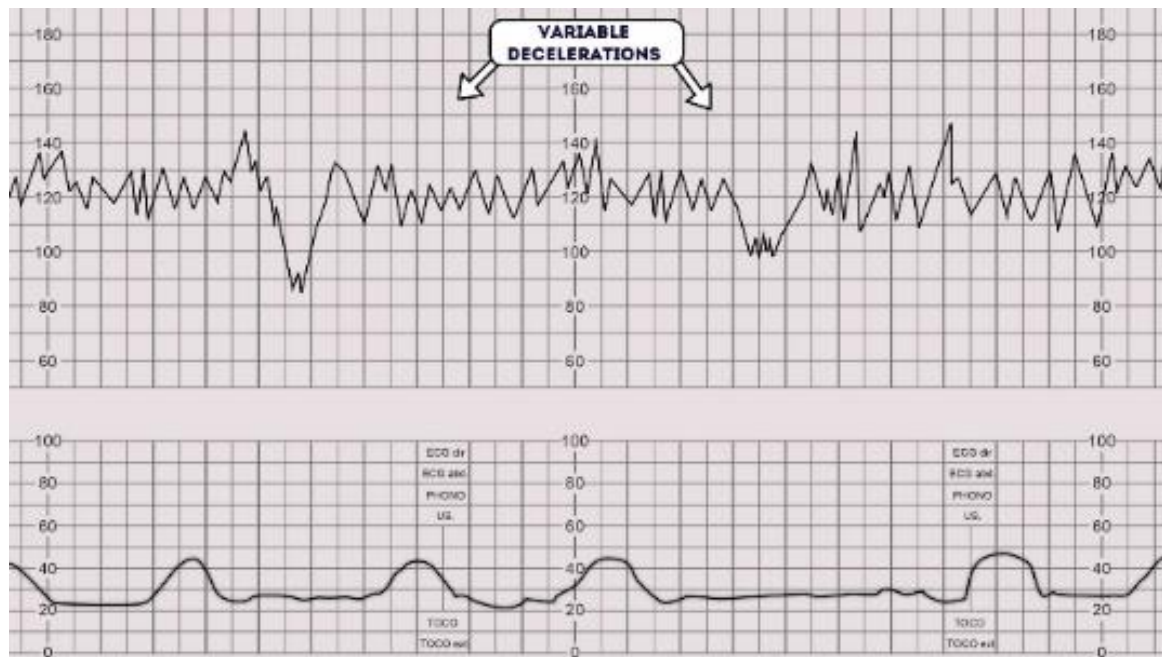


Figure 2.11: Variable Deceleration Signal

➤ Sinusoidal Pattern [10,11]:

The true sinusoidal pattern is rare but highly ominous, associated with elevated rates of fetal morbidity and mortality. This pattern displays a regular, smooth, undulating form resembling a sine wave, with a frequency of two to five cycles per minute and an amplitude range of five to 15 bpm. The baseline heart rate remains stable between 120 and 160 bpm, and there is a lack of beat-to-beat variability. A sinusoidal pattern indicates severe fetal anemia, as seen in cases of Rh disease or severe hypoxia. It is crucial to differentiate the true sinusoidal pattern from the benign "pseudosinusoidal" pattern (Figure 2.12), which exhibits less regularity in shape and amplitude of the variability waves and retains beat-to-beat variability compared to the true sinusoidal pattern.

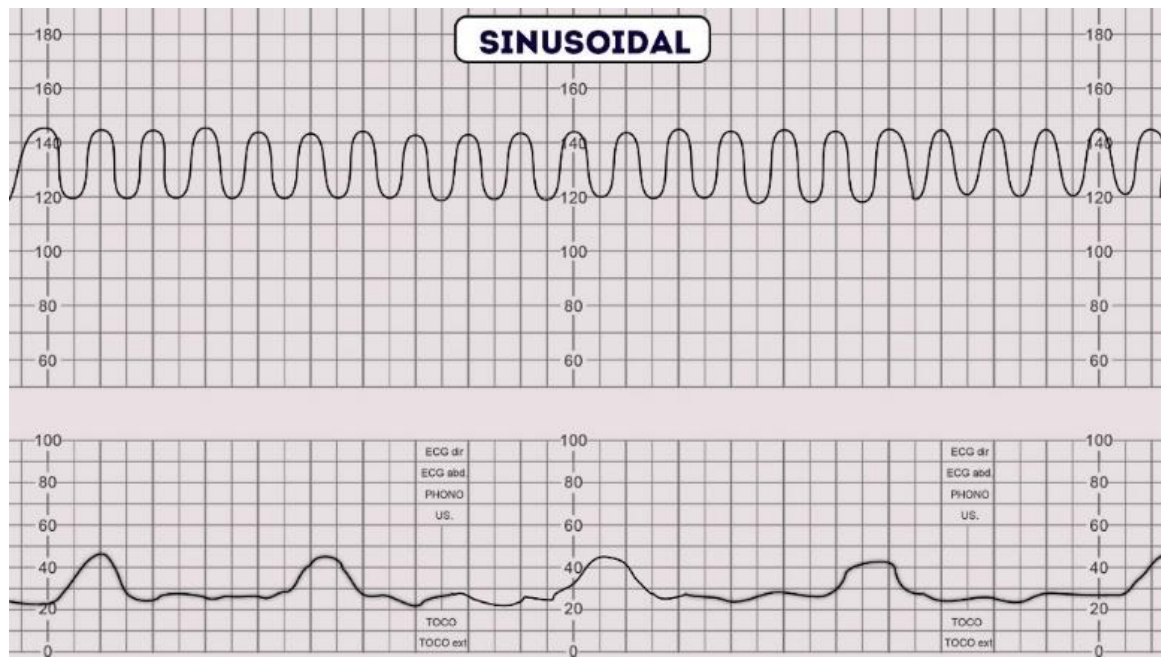


Figure 2.12: sinusoidal signal

2.2 Guidelines for Cardiotocography traces

Since the inception of CTG monitoring, diverse definitions and guidelines have emerged to classify the five key parameters analysed in CTG tracings, namely baseline, variability, accelerations, decelerations, and contractile activity. Numerous countries have implemented classification systems for interpreting CTG patterns. While most guidelines adopt a three-level classification, there are variations in divisions and nomenclature, as outlined in Table 2.1.

The three main classifications for CTG patterns are:

- **FIGO: International Federation of Gynecology and Obstetrics**
FIGO, a global organization headquartered in Switzerland, brings together national societies of obstetrics and gynecology from over 130 countries. With its vast network of experts, FIGO works to improve women's health and rights, advance reproductive medicine, and reduce disparities in healthcare access worldwide. The organization actively advocates for women's health on an international scale, influencing policy, research, and training initiatives that benefit women in diverse cultural and socioeconomic settings.
- **NICE: National Institute of Health and Care Excellence**
NICE, based in the United Kingdom, is a renowned institution known for developing evidence-based guidelines and recommendations to guide healthcare professionals in delivering high-quality, safe, and cost-effective care to patients. The organization's multidisciplinary approach involves collaboration with experts, patients, and other stakeholders to ensure that its guidelines are up-to-date, relevant, and reflective of the latest scientific evidence. NICE has made substantial contributions to various aspects of women's health, including antenatal and intrapartum care, family planning, and gynecological conditions, thereby positively impacting the well-being of countless women in the UK and beyond.
- **ACOG: American Congress of Obstetricians and Gynecologist**
ACOG, based in the United States, is a leading professional association representing obstetricians and gynecologists. With a rich history dating back over a century, ACOG remains at the forefront of women's healthcare advocacy and education. The organization's core mission is to promote excellence in obstetric and gynecological practice, education, and research. ACOG's guidelines and recommendations are highly regarded by practitioners worldwide and serve as a benchmark for quality care in women's health, obstetrics, and gynecology.

FIGO	NICE	ACOG
<i>Normal</i>	<i>Normal</i>	<i>Category I</i>
BHR between 110 and 150 bpm Amplitude of HRV between 5-25 bpm	BHR: 110-160 bpm Variability: ≥ 5 bpm No decelerations There are accelerations	BHR: 110-160 bpm Baseline variability: 6-25 bpm Late or variable decelerations: absent Early decelerations: present or absent Accelerations: present or absent
<i>Suspicious Pattern</i>	<i>Suspicious pattern</i>	<i>Category II</i>
BHR between 150 and 170 bpm or 100 and 110 bpm Amplitude of variability between 5 and 10 bpm for more than 40 min Increased variability above 25 bpm Variable decelerations	BHR: 100-109 bpm or 161-180 bpm Baseline variability < 5 bpm for 40-90 min Decelerations: 1. typical variable decelerations with $>50\%$ of contractions for >90 min 2. single prolonged deceleration for up to 3 min Accelerations: The absence of accelerations with an otherwise normal trace is of uncertain significance	Baseline rate: Bradycardia not accompanied by absent baseline variability or tachycardia. Baseline Variability: minimal variability or absent variability with no recurrent decelerations or marked variability. Accelerations: absence of induced accelerations after fetal stimulation Periodic or episodic decelerations: Recurrent variable decelerations accompanied by minimal or moderate baseline variability. Prolonged deceleration 2-10 min Variable decelerations with other characteristics such as slow return to baseline, overshoots, or shoulders
<i>Pathological Pattern</i>	<i>Pathological pattern</i>	<i>Category III</i>
BHR < 100 or > 170 bpm Persistence of HRV < 5 bpm for >40 min Severe variable of decelerations or severe of repetitive early decelerations Prolonged deceleration Late decelerations: the most ominous trace is a steady baseline variability and with small decelerations after each contraction. Sinusoidal pattern	BHR: <100 bpm or >180 bpm or sinusoidal pattern ≥ 10 min Baseline variability: < 5 bpm for ≥ 90 min Decelerations: 1. a typical variable deceleration with $>50\%$ contractions for > 30 min 2. late decelerations for >30 min 3. prolonged deceleration > 3 min	Absent baseline FHR variability Absent of recurrent late decelerations Absent of recurrent variable decelerations Absent of bradycardia Sinusoidal pattern

Table 2.1: Comparison of CTG classification criteria in FIGO, NICE, and ACOG guidelines.[12]

CHAPTER 3: FETAL HEART RATE VARIABILITY

Fetal heart rate variability (FHRV) is a critical indicator of fetal well-being and physiological adaptability, characterized by fluctuations in the fetal heart rate over time. It serves as a valuable tool in assessing fetal health during pregnancy, influenced by factors like fetal movements, autonomic nervous system regulation, and responses to external stimuli. Monitoring FHRV is essential in both low-risk and high-risk pregnancies for the early detection of fetal distress and timely intervention [5,9].

The regulation of the fetal heart rate (FHR), akin to adults, involves both the autonomic and somatic components of the central nervous system. The autonomic component comprises the sympathetic and parasympathetic systems, with the sympathetic system increasing heart rate and the parasympathetic system decreasing it. Their interplay gives rise to baseline FHR variability observed in CTG traces. In contrast, the somatic component, governing voluntary body movements, results in accelerations on the CTG trace [5,9].

Research in fetal sheep, commonly used as a model for cardiovascular physiology, reveals developmental changes in the autonomic nervous system's influence on cardiovascular homeostasis. Alpha-adrenergic and ganglionic blockade has a more significant impact on blood pressure in term fetal sheep compared to preterm ones. Newborn lambs exhibit reduced susceptibility to these blockades, which further diminishes with postnatal development. Late in gestation, fetal sheep exhibit pronounced sympathetic noradrenergic and peptidergic tone, counterbalanced by nitric oxide (NO) dilator tone to maintain arterial pressure. [5,9]

Additionally, parasympathetic function, particularly in heart rate regulation, undergoes maturation. Cholinergic blockade affects heart rate differently in premature fetal sheep, term fetuses, and postnatal lambs. Studies on preterm and term infants show an increase in parasympathetic modulation of heart rate during the first six months of life, with preterm infants displaying less modulation at similar postnatal ages [5,9].

Arterial pressure exhibits physiological variability in both fetal and postnatal life. In term fetal sheep, ganglionic blockade significantly reduces heart rate and arterial pressure variability. Basal sympathetic tone, recorded from the renal sympathetic nerve, correlates with normal fluctuations in heart rate and arterial pressure, associated with changes in fetal behavioral state. Sleep-state-dependent changes in hemodynamics and resting renal sympathetic nerve activity (RSNA) have been observed

in near-term sheep fetuses, reflecting varying autonomic activity. Various physiological parameters, including organ blood flows, regional vascular resistances, and cerebral oxygen consumption, are influenced by electrocortical state and likely indicate changes in autonomic activity [5,9].

Understanding developmental cardiac electrophysiology necessitates considering the maturation of the autonomic nervous system and its impact on cardiac electrophysiological properties. The autonomic nervous system plays a pivotal role in modulating pacemaker impulse generation, atrioventricular (AV) conduction, and myocardial refractoriness [5,9].

In terms of the parasympathetic nervous system, progressive increases in choline acetyltransferase concentration and cholinergic innervation density occur during development. Muscarinic receptors are present before actual innervation, becoming denser in regions like the sinoatrial and AV nodes and throughout the atria. Acetylcholine, the primary parasympathetic neurotransmitter, influences cardiac ion channels, increasing outward potassium currents and hyperpolarizing cells, leading to pacemaker rate slowing. Acetylcholine also inhibits the "funny pacemaker current" (I_f), contributing to pacemaker slowing [5,9].

The maturation of parasympathetic control is evident in heart rate variability and responses to muscarinic stimulation during development. While parasympathetic responses exist in utero and in preterm infants, significant maturation occurs postnatally, affecting both the magnitude and type of responses to parasympathetic stimulation [5,9].

Regarding the sympathetic nervous system, the early mammalian heart shows functional modulation of calcium channel currents by β -adrenergic receptors before sympathetic innervation. However, the sympathetic system is less developed at birth compared to the parasympathetic system in many mammalian species, including humans. Rapid maturation of sympathetic innervation occurs within the first few months postnatally. With maturation, the electrophysiological responses to catecholamine stimulation change. Sympathetic stimulation influences heart rate, myocardial refractoriness, and conduction. Responses to sympathetic stimulation become more pronounced with maturation, influenced by increasing sympathetic innervation density and postnatal upregulation of stimulatory effects on adenylate cyclase [5,9].

Complex interactions between the sympathetic and parasympathetic branches impact heart rate control, with muscarinic-mediated stimulation of phosphatases potentially reversing adrenergic-stimulated phosphorylation of intracellular proteins, including calcium channels. Nitric oxide, derived

from l-arginine, also plays a role in cholinergic inhibition of β -adrenergic responses. These interactions are more pronounced during development, with sympathetic-vagal interactions observed even in neonates, where sympathetic effects become less pronounced with higher levels of background vagal stimulation [5,9].

Furthermore, besides the classic autonomic neurotransmitters acetylcholine and norepinephrine, neuropeptides also innervate the human heart. These peptides, including neuropeptide Y, vasoactive intestinal peptide, calcitonin gene-related peptide, somatostatin, and substance P, may co-localize with classic neurotransmitters or exist in neurons separate from the main autonomic branches. They exert direct or indirect effects on cardiac automaticity and conduction. Neuropeptide Y functions as a sympathetic co-transmitter, while vasoactive intestinal peptide increases sinoatrial node automaticity and enhances AV nodal conduction. The presence and function of these neuropeptides in the fetal heart develop during gestation and early postnatal life [5,9].

3.1 Techniques Analysis

Techniques for analysing FHRV have evolved over the years, thanks to advances in technology and research. Traditionally, FHRV was assessed visually through cardiotocography (CTG), a method that visually displays the fetal heart rate and uterine contractions on a paper strip. However, with the emergence of computerized systems and digital technology, computerized cardiotocography (cCTG) has become more prevalent. cCTG offers enhanced accuracy and provides various computer algorithms to analyse FHRV patterns objectively.

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3.1.1 Time Domain Analysis

There are many parameters used to analyse FHR signals; in the case of time domain analysis, it's commonly used the mean, and standard deviation, but there are other indices used, like, short-term variability (STV), long-term variability (LTV), interval index (II), long-term irregularity (LTI). [13,14]

- In the case of STV, there are different formulas applied in clinical studied and they are easily used in the case of CTG data systems[13,14]:

- a. Arduini quantifies STV as mean of absolute beat to beat difference (3.1):

$$STV = \sum_{i=1}^{k-1} \frac{|T(i+1) - T(i)|}{k-1} \quad (3.1)$$

where k is number of samples in 60s, T(i) represents the instantaneous inter-beat intervals expressed in milliseconds.

- b. Dalton quantifies STV as absolute beat to beat difference (3.2):

$$STV = \sum_{i=1}^n \frac{|T(i) - T(i-1)|}{2} \quad (3.2)$$

Where n is number of beats in 60s, T(i) represents the instantaneous inter-beat intervals expressed in milliseconds.

- c. Organ quantifies STV as instantaneous variability (3.3):

$$STV = \sum_{i=1}^n \frac{|F(i+1) - F(i)|}{n} \quad (3.3)$$

Where n is number of beats in 30s, F(i) is the instantaneous FHR expressed in beats per minute (bpm) and obtained as $\frac{60000}{T(i)}$, with T(i) represents the instantaneous inter-beat intervals expressed in milliseconds.

- d. Redman saw STV as “epoch to epoch variation” (3.4):

$$STV = \frac{1}{15} \sum_{m=1}^{15} |R(m+1) - R(m)| \quad (3.4)$$

Where R(m) is calculated as (3.5):

$$STV = R(m) = \sum_{i=1}^r \frac{|T(i+1) - T(i)|}{r} \quad (3.5)$$

Where r is the number of RR intervals in 3.75s, $\frac{1}{15}$ signifies the number of subintervals in 60s.

e. Vain Geijn saw STV as interval difference (3.6):

$$STV = IQR[g_i * (T(i) - T(i-1))] \quad (3.6)$$

Where $g_i = \sqrt{\frac{180}{\bar{T}_i - 320}}$:= weighting factor where $\bar{T}_i = \frac{T(i-1) + T(i)}{2}$; IQR, i.e., interquartile range, computed 30s

f. Yeh sees STV as differential index (3.7):

$$STV = \sqrt{\sum_{i=1}^{n-1} \frac{(D(i) - D_{ave})^2}{n-2}} \quad (3.7)$$

Where $D_i = 1000 * \frac{T(i) - T(i+1)}{T(i+1) + T(i)}$ $D_{ave} = \frac{\sum_{i=1}^{n-1} D(i)}{n-1}$ $n = \text{number of beats in 60s}$

g. Zugaib proposes a formula (3.8):

$$STV = \frac{1}{n-1} * \sum_{i=1}^{n-1} |V(i) - Md| \quad (3.8)$$

Where $V_i = \frac{T(i+1) - T(i)}{T(i+1) + T(i)}$, $n=128$ beats, Md =median of V_i

h. Cesarelli proposed a formula which it now seen as the standard deviation of FHR (3.9):

$$SD = \sqrt{\frac{1}{n-1} \sum_{i=1}^n (F(i) - \bar{F})^2} \quad (3.9)$$

Where n is the number of beats in 60s and F is the mean of FHR signals.

The advantage of using STV is connected to the development of metabolic academia, and it is recognized as a valuable antenatal monitoring tool; but the problem using this method is that there is no agreement on formula used to calculate the STV, its effectiveness can be influenced by frequency oscillations. [13,14]

- LTV shows good sensitivity to sinusoidal fluctuations in the heart rhythms, but it can be difficult to quantify numerically.
- In the cases of LTI and II indices, their formulas were proposed by Esposito et al. (3.10) and (3.11):

$$LTI = m_{24}(j) = \sqrt{T_{24}^2(j) + T_{24}^2(j+1)} \quad (3.10)$$

Defined as the interquartile range $(\frac{1}{4}; \frac{3}{4})$ of distribution of the modal $m_{24}(j)$ computed on a 3 min segment of inter-beat sequence $T_{24}(i)$ with $i=1, \dots, 72$.

$$II = \frac{std[T_{24}(i+1) - T_{24}(i)]}{STV} \quad (3.11)$$

Calculated as the coefficient of variation between the differences of all FHR values in 1 min of inter-beat sequence $T_{24}(i)$ in ms, with $i=1, \dots, 23$, taken each 25s.

3.1.2 Frequency Domain Analysis

Frequency domain analysis involves assessing the individual contributions of different frequency components to the overall heart rate fluctuation. This analysis entails calculating the spectral energy content of each frequency component using a technique called power spectral analysis (PSA). [13]

PSA is utilized as a predictive tool in studying adult cardiac functions and has also been applied to analyse fetal heart rate variability (FHRV). In comparison to time domain measurements, PSA not only provides information about frequency distribution but also quantifies the extent of heart rate variations due to the relationship between power and amplitude. [13]

Just like in the analysis of adults' heart rate variability (HRV), the fetal heart rate variability (FHRV) analysis also typically involves considering three frequency bands with varying ranges. These bands

are: Very Low Frequency (VLF: 0–0.05 Hz), Low Frequency (LF: 0.05–0.2 Hz), which is associated with sympathetic control and vasomotor activity, and High Frequency (HF: 0.2–1 Hz), driven by respiration and influenced by vagal activity. It's worth noting that there is still no consensus in the literature regarding the precise range of values for each spectrum band, as previously discussed in a prior review. Additionally, in some studies, an alternative spectral band is sometimes considered, which relates to fetal movements and the mechanical effects of maternal breathing, known as the Movement Frequency (MF: 0.15–0.5 Hz). [13]

The ratio between LF and HF, or the sum of HF + MF when the latter is considered, serves as an index of the balance between the cardiac physiological control components (controlled by the two branches of the autonomic nervous system) and the fetus's activity level (sympatho-vagal balance).

The primary and widely used method for analysing fetal heart rate variability (FHRV) is Fourier analysis. This technique involves breaking down the FHR signal into sinusoidal components. Since the FHR signal is inherently discrete due to sampling, the discrete Fourier transform (DFT) is employed to represent the original FHR sequence in the discrete frequency domain. The Fast Fourier Transform (FFT) is a commonly used algorithm to efficiently compute the DFT, often applied to short time scales where the FHRV signal exhibits stationarity. Typically, a signal segment of 32 s is chosen for this purpose. [13]

However, when dealing with non-stationary RR (R-R interval) sequences, the assumptions underlying spectral analysis methods are no longer valid. To handle non-stationary conditions, various techniques for time-frequency analysis have been developed. Among these, the Short-Time Fourier Transform (STFT) stands out as a variation of the Fourier transform, specifically well-suited for non-stationary signals. The STFT divides the signal into specific periods of constant length and applies the Fourier transform individually to each of these segments of the signal. The STFT is mathematically represented as (3.12):

$$X(\tau, \omega) = STFT\{x(t)\} = \int_{-\infty}^{+\infty} x(t) \omega(t - \tau) e^{-j\omega t} dt \quad (3.12)$$

The provided formula employs a windowing function $w(t)$ (typically a Hanning or Gaussian function) to multiply the signal $x(t)$ before transformation. As the windowing function shifts along the time axis, the resulting signal undergoes local transformation. This process yields a two-dimensional function

$X(\tau, \omega)$, which represents the Fourier Transform of $x(t)$ multiplied by $w(t - \tau)$. The resulting function $X(\tau, \omega)$ reveals both the phase and magnitude of the original signal $x(t)$ across different time intervals and frequencies.

Due to its simplicity and minimal computational power requirements, this method is extensively utilized in the literature.

Variations in the FHRV spectrum are influenced by specific factors such as the cord arterial base deficit, changes in behavioural state, and gestational age.

Maintaining stationarity in the FHRV signal is crucial for accurate analysis.

This method has limitations in accurately describing the nonlinear structure of sympatho-vagal interactions.

The frequency resolution is influenced by the length of data segments used in the analysis. Another approach to analyse fetal heart rate (FHR) can be found in the use of AR (AutoRegressive) models, which offer improved identification of discrete frequency oscillations in time series and have been widely applied in the analysis of heart rate variability (HRV) and fetal heart rate variability (FHRV).

An AR series is represented by the following equation (3.13):

$$X(n) = - \sum_{k=1}^p a_k * x(n) + e(n) \quad (3.13)$$

Here, $x(n)$ is the input signal, p is the model order, a_k are the AR model parameters, and $e(n)$ represents the error, which is a zero-mean white Gaussian noise.

Despite their widespread use, the effectiveness of AR models largely depends on selecting an appropriate model order. Using low-order AR models may limit a comprehensive representation of the FHR signal properties, whereas a high-order AR model could be preferred. Higher-order AR models, due to their increased degrees of freedom, can better capture the complexities of the time series and provide a more accurate fit to the data. [13]

Akaike's Information Criterion (AIC) is among the numerous criteria used to estimate the appropriate model order for AR (AutoRegressive) models, and it is widely utilized for this purpose. It determines the order of the AR model by minimizing the following function (3.14):

$$AIC(p) = N * \ln \sigma_p^2 + 2 * p \quad (3.14)$$

Here, N represents the number of data points, and σ_p^2 is the mean squared error calculated as (3.15):

$$\sigma^2 = \frac{1}{N} \sum_{p=1}^{N-1} e^2(n) \quad (3.15)$$

In a study conducted by Bracale et al., they analysed 50 real CTG recordings using AR models with orders ranging from 4 to 14. The best order was chosen based on the AIC function and the whiteness test. Once the AR coefficients were determined, they calculated the Power Spectral Density (PSD) of the FHRV as (3.16):

$$S(f) = \frac{\sigma^2 T}{\left[1 - \sum_{k=1}^p a_k e^{-j2\pi f k T}\right]^2} \quad (3.16)$$

Where T represents the sampling period. Their analysis indicated that an order of eight was the optimal choice to estimate the PSD of the FHRV for all signals under study. [13]

AR models provide better identification of discrete frequency oscillations for non-stationary and relatively short data records (usually acceptable in the range of 30 s to 60 s duration). On the other hand, Fourier analysis is more suitable for relatively stationary data records lasting more than 250 s. Fourier analysis allows searching for very-low-frequency oscillations and performs better as an amplitude estimator when reporting the percent power in various frequency bands. [13]

In 1989, Ansourian et al. presented a digital analysis using AR power spectral estimation with an optimized Burg algorithm. This approach demonstrated good modelling of short-time series, potentially useful in monitoring fetal breathing movements, and offered higher resolution compared to the classical FFT, despite increased computational complexity. In 2001, Cazares et al. utilized an AR model of uterine activity (UA) to estimate the power at the contraction frequency. The results, based on 12 intrapartum UA traces, were compared with visual inspection by experts, confirming that the proposed tenth-order AR model, with an agreement percentage of 62%, could serve as a helpful confidence index for the automated assessment of UA, potentially reducing errors in the identification

of uterine contractions. More recently, Fuentealba et al. proposed a time-varying AR model to analyse the spectral dynamical changes in the FHR signal over time. They revealed that certain time domain alterations could lead to significant dynamical frequency domain changes. Particularly, decelerations leave singular spectral traces, the characteristics of which could aid in distinguishing between normal and pathological fetal conditions. [13]

Wavelet transform (WT) is particularly useful for analysing non-stationary signals or those containing multiple components, making it valuable in processing medical and biological signals. For FHR analysis, WT has proven helpful in investigating the long-term non-stationary behaviour of FHR.

The algorithm involves convoluting "local" wavelike functions, known as wavelets, with the signal of interest. This process is mathematically expressed as follows (3.17):

$$W_s(a, b) = \int_{-\infty}^{+\infty} s(t) \psi_{a,b}^*(t) dt \quad (3.17)$$

In this equation, $s(t)$ represents the time domain signal, $*$ denotes the complex conjugate, and $\psi_{a,b}(t)$ is the mother wavelet scaled by a factor of a ($a > 0$) and dilated by the factor b , defined as (3.18):

$$\psi_{a,b}(t) = \frac{1}{\sqrt{a}} \psi_{a,b} \left(\frac{t-b}{a} \right) \quad (3.18)$$

Choosing the appropriate type and width of the mother wavelet, i.e., one that matches the shape of the original signal at a specific scale and location, is crucial for an effective transformation of the signal, as this directly affects the analysis performance. [13]

WT is commonly used to estimate the energy distribution of a signal by calculating the standard deviation of the wavelet coefficients in different frequency ranges of the FHR. This allows selecting the appropriate scale in the wavelet transform, where smaller scales correspond to more rapid variations and higher frequencies, while disregarding the contribution of other scales. [13]

Wavelet transform has been applied for various purposes, such as predicting perinatal outcomes and discriminating normal pregnancies from those complicated by gestational hypertension or gestational diabetes. Both studies showed that parameters extracted from the wavelet domain reveal hidden information from FHR signals. [13]

Vasios et al. proposed an automated method to support early diagnosis of fetal hypoxia using WT and self-organizing-map neural networks to analyse and classify FHR and fetal pulse oximetry signals. WT facilitated proper processing of the FHR signal, addressing the issue of long-term non-stationary behaviour, and extracting FHR power at different scale levels, which were used as input to the neural networks along with pulse oximetry data. The classification results demonstrated good sensitivity (83%) and specificity (96%) in categorizing FHR patterns. [13]

Similarly, Salamaleki et al. tackled the problem of fetal hypoxia using the same system as previously described by Vasios et al. They confirmed that computerized analysis of FHR and pulse oximetry based on the combination of WT and artificial neural networks (ANN) could yield promising results in terms of sensitivity (83.3%) and specificity (97.9%) for intrapartum diagnosis of hypoxic fetuses. [13]

3.1.3 Nonlinear Techniques

Time and frequency analyses of fetal heart rate (FHR) have proven to be valuable in assessing fetal heart rate variability (FHRV). However, these linear methods have significant limitations. Time domain indices mainly rely on descriptive statistical measurements of the FHR signal and cannot infer the physiological processes controlling heart rhythm variations. On the other hand, frequency domain approaches are sensitive to artifacts and do not allow the examination of non-periodic trends embedded in the variability signal. This lack of insight into complex mechanisms underlying heart rate variability hinders a proper understanding of fetal health status and reliable risk stratification. Moreover, linear techniques used to characterize FHRV, like adult heart rate variability (HRV), are fundamentally limited in their ability to describe the nonlinear structure of underlying sympatho-vagal interactions. [13,14]

To explore these hidden phenomena, which are crucial for a comprehensive description of FHR variability, alternative methodologies called "nonlinear techniques" have been developed. These techniques encompass algorithms and approaches that quantify non-periodic contributions to FHR signals' variability and classify them accordingly. Nonlinear techniques can be used alone or in combination with traditional time and frequency domain analyses to gain a deeper understanding of FHR dynamics. [13,14]

Shannon proposed that the information contained in a signal can be precisely quantified as the quantity of unexpected data in the message, a concept termed entropy. Entropy is a probabilistic measure of complexity, frequently utilized in analysing physiological signals to quantify the irregularity of time series data. Several entropy measures have been widely employed in this context, including

Shannon entropy (SE), approximate entropy (ApEn), sample entropy (SampEn), and multiscale entropy (MSE). [13,14]

- In 1948, Shannon (40) introduced the concept of entropy (Shannon entropy- SE) as a measure to precisely quantify the information within a signal. It assesses the amount of unexpected data present in the message. The calculation of Shannon entropy is as follows (3.19):

$$SE = - \sum_i p(x(i)) * \log(p(x(i))) \quad (3.19)$$

Where $p(x(i))$ represents the probability of the point $x(i)$, of a time series $X = (x_1, x_2, \dots, x_N)$

- In 1991, Pincus et al. developed a regularity statistic tool to quantitatively assess the level of regularity and unpredictability in time-series data fluctuations. This tool, known as approximate entropy (ApEn), is based on the premise that healthy dynamic stability arises from specific mechanisms and properties within networks. However, when vulnerable connections emerge between systems or within one system, it indicates a disease mechanism, which is characterized by an increase in the regularity of the series. [13,14]

To compute ApEn for a given time series $X = (x_1, x_2, \dots, x_N)$, a new series of vectors of length m (embedding dimension), $X_m(i) = (x_i, x_{i+1}, x_{i+2}, \dots, x_{i+m-1})$, is constructed for each $i = 1, \dots, N - m + 1$. For each vector $X_m(i)$, the value $C_m^r(i)$ is calculated, where r is referred to as the tolerance value. The computation of $C_m^r(i)$ is as follows (3.20):

$$C_m^r(i) = \frac{\text{number of } d[X_i, X_j] \leq r}{N - m + 1}, \forall j \quad (3.20)$$

The distance between the vector $X_m(i)$ and its neighbour $X_m(j)$ is defined as (3.21):

$$d[X_m(i), X_m(j)] = \max_{k=1, \dots, m} |x(i + k - 1) - x(j + k - 1)| \quad (3.21)$$

The average of natural logarithm of $C_m^r(i)$ is computed for all i (3.22):

$$\Phi_m^r = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} \ln(C_m^r(i)) \quad (3.22)$$

Since in practice N is a finite number, the statistical estimate is computed as (3.23):

$$ApEn(m, r) = \begin{cases} \phi_m^r - \phi_{m+1}^r, & m > 0 \\ -\phi_1^r, & m = 0 \end{cases} \quad (3.23)$$

Regarding ApEn, the most used value for the embedding dimension is $m = 2$. Nonetheless, various algorithms have been proposed to estimate the smallest sufficient embedding dimension, m . One frequently employed method is the "false nearest neighbours" algorithm, suggested by Kennel et al. However, this method has a limitation as it relies on the subjective definition of false neighbours. To address this limitation, Cao introduced a new method. [13,14]

To determine an appropriate time delay for the analysis, different approaches have been suggested. The two most used methods are the autocorrelation function and the average mutual information function. Pincus and Goldberger recommend choosing values between 10% and 25% of the standard deviation of the data to achieve a scale-invariant measurement. Some researchers have also achieved success using a fixed r value. However, in such cases, the entropy values often exhibit high correlation with the time series standard deviation. [13,14]

Lu et al. demonstrated that ApEn values can vary significantly even within the defined range of r values. They presented a new method for automatically selecting the r value corresponding to the maximum ApEn value.

- In 2000, Richman and Moorman introduced the sample entropy (SampEn) as an alternative to ApEn, with the same objective of evaluating the randomness of biological time series, particularly HR time series. The main limitation of ApEn lies in its dependence on the record length, resulting in lower ApEn values for short records. Moreover, if one time series exhibits higher ApEn than another under certain conditions, it may not hold true for all conditions. To address these limitations, the authors proposed a new family of statistics called SampEn(m, r), which reduces bias, particularly in short data sets, by implementing the following changes:
 1. Self-matches are not counted.
 2. Only the first N -vectors of length are considered.
 3. Conditional probabilities are not estimated in a template manner.

To calculate the value of SampEn, the parameters m and r defined for ApEn are required. Using A to denote the number of vector pairs of length $m + 1$ having $d[X_m(i), X_m(j)] \leq r$, with $i \neq j$, and B as the total number of templates matches of length m , also with $i \neq j$, the SampEn is determined by the equation (3.24):

$$SampEn = -\ln\left(\frac{A}{B}\right) \quad (3.24)$$

This probability measure is directly computed as the logarithm of the conditional probability and not from the logarithmic sums ratio, demonstrating relative consistency in cases where ApEn does not exhibit such consistency. [13,14]

3.2 Fetal Heart rate and Hypoxia

Fetal hypoxia refers to a condition in which the developing fetus experiences an inadequate supply of oxygen during its time in the womb. This can occur due to various factors, including maternal health issues, placental problems, or complications in the fetal cardiovascular system. Fetal heart rate variability (FHRV) is an essential parameter that reflects the fluctuations in the fetal heart rate and is considered an indicator of the fetal autonomic nervous system's development and overall health. [15]

The main premise of electronic fetal heart rate (FHR) monitoring is that a normal FHR pattern suggests the fetus is not hypoxic or acidotic at that moment. However, when the FHR is abnormal, it does not necessarily mean the fetus is in distress or significantly acidotic at birth. The term "fetal distress" has been replaced with "no reassuring fetal status" to avoid ambiguity. [15]

Different terms like "fetal distress," "fetal asphyxia," and "asphyxial trauma" are often used interchangeably, causing confusion for healthcare providers. Asphyxia refers to a lack of oxygen resulting in metabolic acidosis in the fetus but does not always lead to fetal morbidity or mortality. [15]

The American College of Obstetricians and Gynecologists established specific criteria to establish an acute intrapartum event that could cause cerebral palsy. These criteria include evidence of metabolic acidosis in fetal umbilical artery blood at birth, early onset of severe or moderate encephalopathy, and exclusion of other identifiable causes.[15]

The goal of FHR monitoring is to detect fetal hypoxia early and attempt to prevent asphyxic damage resulting from prolonged and severe hypoxia. Normal FHR patterns, including accelerations and normal variability, are associated with good outcomes. Abnormal patterns may indicate hypoxia and should be managed with appropriate interventions. Tachycardia may be a result of hypoxia, but associated decelerations are the first indicators of hypoxia. [15]

There are specific patterns that can be related to hypoxia, which we have seen in chapter 2.1, but we'll see them in from the point of view of hypoxia:

- Late Decelerations [16]

Late decelerations are visually apparent, usually symmetrical, gradual decreases, and returns of the fetal heart rate (FHR) associated with uterine contractions. The FHR decrease from the onset to the nadir of the deceleration lasts for 30 s or more. Late decelerations are delayed in timing, with the

nadir occurring after the peak of the contraction. They are often found in association with uteroplacental insufficiency and suggest some degree of fetal hypoxia.

In their mildest form, late decelerations are associated with normal or increased FHR variability and appear consistently from one contraction to the next. Intervention measures such as optimizing uterine blood flow, lateral position, hydration, and supplemental oxygen can be used when intermittent late decelerations with good variability are observed. Persistent late decelerations with complete absence of variability are more ominous and often indicate fetal acidosis. In such cases, expedited delivery, often via cesarean section, is recommended. [15]

Excessive uterine stimulation, such as from oxytocin administration, is a common cause of late decelerations. Discontinuation or careful reinitiation of oxytocin at a lower rate can improve the FHR pattern. In some cases, late decelerations may persist despite oxytocin discontinuation, and the fetus may show intolerance to labor. Close monitoring of the fetus is needed in such cases, and expedited delivery may be required if signs of acidosis are present. [15]

Management of late decelerations requires continuous monitoring and clinical judgment to ensure the best possible outcome for both the fetus and the mother.

- Variable Decelerations [16]

Variable decelerations are visually apparent, abrupt decreases in fetal heart rate (FHR) associated with uterine contractions. They are most frequently caused by umbilical cord compression and can vary in depth and duration. Variable decelerations can be non-reassuring if they last more than 40 to 60 s on a repetitive basis, have a slow return to baseline, show an increasing baseline heart rate, or exhibit decreasing FHR variability.

The management of variable decelerations depends on their characteristics and severity. Reassuring variable decelerations can be closely monitored and allowed to continue, while non-reassuring patterns may require intervention. Various causes of variable decelerations, such as oligohydramnios, nuchal cords, cord prolapse, and cord entanglement, may necessitate different management approaches.

Prophylactic and therapeutic amnioinfusion can help decrease the frequency of variable decelerations and facilitate management decisions. Proper understanding and assessment of variable decelerations are crucial to avoid unnecessary cesarean sections and ensure optimal outcomes for both the fetus and the mother.

- Prolonged Decelerations [16]

Prolonged decelerations in fetal heart rate (FHR) are visually apparent decreases below the baseline, lasting 2 min or more but less than 10 m, with a decrease of 15 bpm or more. If the deceleration lasts 10 min or longer, it is considered a baseline change.

Prolonged decelerations can occur as isolated events and may have identifiable causes or occur without apparent etiology. Potential causes of prolonged decelerations include hypertonic or prolonged contractions, vaginal examination, application of internal fetal scalp electrode, fetal scalp blood sampling, prolapsed umbilical cord, maternal seizure, epidural or spinal block, supine hypotension, fetal central nervous system anomalies, prolonged umbilical cord compression, maternal respiratory arrest, uterine rupture, and abruptio placentae.

When prolonged decelerations occur after conduction anesthesia, the initial management should focus on correcting maternal hypotension by repositioning the patient, providing IV fluids, and administering oxygen. If necessary, IV ephedrine and tocolytic agents may be used to address tetanic contractions and prolonged FHR decelerations.

The clinical response to prolonged decelerations should be cautious, allowing some time for spontaneous recovery. A vaginal examination is performed to identify rapid descent and impending delivery or a prolapsed cord as potential causes. A thorough review of the patient's clinical status and fetal monitor data is essential to identify treatable causes and ensure a positive outcome. [16]

CHAPTER 4: ANALYSIS OF HEART RATE VARIABILITY

4.1 Data

This thesis presents a comprehensive study on neonatal health assessment through the analysis of Cardiotocography (CTG) recordings and associated clinical parameters. The research is based on a dataset sourced from the Czech Technical University (CTU) in Prague and the University hospital in Brno (UHB), accessible through the physionet website. The dataset comprises 552 CTG recordings, carefully selected from a larger pool of 9,164 recordings spanning the years 2010 to 2012 at UHB. Each recording, with a duration of approximately 90 min, encompasses fetal heart rate time series, uterine contractions signal, maternal delivery details, and fetal clinical data.

The assessment of neonatal health is of paramount importance, and it presents one of the primary challenges of our time. Neonatal mortality accounts for a significant portion of child deaths, prompting global initiatives like the Millennium Development Goals to address the need for improved strategies in promoting neonatal health. To achieve this goal, the development of innovative tools and technologies for fetal, maternal, and neonatal care has been a focus of research and practice.

The CTG recordings in this study were initiated during the final stages of labor and continued for 90 min. These recordings included the fetal heart rate (FHR) time series and uterine contractions (UC) signal, both sampled at a rate of 4 Hz. Stringent criteria were employed to ensure data homogeneity, including requirements for singleton pregnancies, gestational age exceeding 36 weeks, the absence of known defects prior to pregnancy, limited duration of the second stage of labor, high FHR signal quality, and availability of biochemical parameters from umbilical arterial blood samples. A predominance of vaginal deliveries was also a key criterion, with only 46 cases of caesarean section (CS) deliveries included in the dataset.

Supplementary parameters were collected from text files and incorporated into the analysis, encompassing maternal data (e.g., age, parity, gravidity), delivery data (e.g., type and duration of delivery, presence of meconium-stained fluid, measurement methods), fetal data (e.g., sex, birth weight), and fetal data outcomes (e.g., umbilical artery blood sample analysis including pH, pCO₂, pO₂, base excess, computed BDecf, and Apgar score).

4.2 Method

The analysis was conducted using MATLAB, with the inclusion of the HRV path for analysis, and EXCEL. The dataset was organized into a table with 552 rows and 7 columns, including parameters such as mean NN intervals (i.e., represents RR intervals normalised), standard deviation of NN intervals, absolute power in various frequency ranges (VLF, LF, HF), LF/HF ratio, and TINN (Triangular Interpolation of NN intervals).

Additional columns were added from text files, encompassing parameters like pH (measure of blood acidity/alkalinity), BE (measure of base excess/deficit in the blood), and Apgar5 (quick assessment of newborn's physical condition which was done in 5 min). The table initially contained NaN (not a number) values, which were subsequently removed, resulting in the analysis being conducted on 395 subjects.

The assessment of neonatal health typically relies on clinical parameters such as blood pH, BE, and Apgar5. However, these parameters may provide conflicting information about the newborn's clinical condition. To address this, sub-tables were created to identify hypoxic and non-hypoxic patients based on specific criteria ($\text{pH} < 7.1$, $\text{BE} < -10 \text{ mmol/l}$, $\text{Apgar5} < 7$).

Statistical tests were employed to compare hypoxic and non-hypoxic subjects. Due to the non-normal distribution of data, the Mann-Whitney U test was used for statistical analysis. Additionally, the distribution of features was analysed by calculating the 25th, 50th, and 75th percentiles to gain insights into feature concentration within the dataset.

4.3 Results

This section presents the key findings of our study, focusing on three essential features—pH, base excess (BE), and Apgar score at 5 minutes (Apgar5)—as diagnostic parameters for neonatal hypoxia. The following three tables provide a comprehensive overview of these features, including the number of healthy and pathological neonates, percentile distributions, and corresponding p-values, shedding light on their diagnostic potential.

Table 4.1 showcases the diagnostic potential of pH as a critical parameter for neonatal hypoxia identification. It includes the number of healthy and pathological neonates, the distribution of percentiles, and the p-value associated with pH measurements. This table provides insights into the relationship between pH levels and neonatal health.

In Table 4.2, we delve into the diagnostic capabilities of base excess (BE) in distinguishing between healthy and pathological neonates. This table presents the number of neonates in each category, percentile distribution of BE values, and the corresponding p-value. It offers a comprehensive understanding of BE as a diagnostic parameter for neonatal hypoxia.

Table 4.3 evaluates the performance of Apgar score at 5 minutes (Apgar5) as a diagnostic indicator for neonatal hypoxia. It provides a breakdown of neonates by health status, percentile distribution of Apgar5 scores, and the associated p-value. This table offers insights into the utility of Apgar5 in neonatal hypoxia identification.

These tables serve as essential references for assessing the diagnostic potential of each feature, helping to elucidate their roles in identifying neonatal hypoxia. The percentile distributions and p-values provide valuable statistical insights, contributing to a comprehensive understanding of these parameters in neonatal healthcare.

Gold Standard: pH					
	#	DISEASED	#	HEALTHY	P value
Mean NN	35	456[432;494]	356	457[434;488]	0.93
SD NN	35	106[89;137]	356	79[59;101]	2.27E-06
VLF power (bpm ²)	35	30901[14787;48712]	356	21118[12857;34464]	0.11
LF power (bpm ²)	35	1807[785;3145]	356	1670[975;2507]	0.67
HF power (bpm ²)	35	17[10;29]	356	15[10;25]	0.68
LF/HF ratio	35	89[61;140]	356	100[67;157]	0.52
TINN	35	109[51;141]	356	102[78;141]	0.45

Table 4.1: results according to pH

Gold Standard: BE					
	#	DISEASED	#	HEALTHY	P value
Mean NN (mmol/l)	53	456[433;495]	342	457[433;488]	0.73
SD NN (mmol/l)	53	100[80;49648]	342	79[60;101]	0.0001
VLF power (bpm ²)	53	30117[1302;49648]	342	20689[13200;33730]	0.05
LF power (bpm ²)	53	1834[959;3108]	342	1666[971;2487]	0.43
HF power (bpm ²)	53	17[9;22]	342	15[10;25]	0.89
LF/HF ratio	53	109[72;170]	342	97[67;155]	0.62
TINN	53	117[55;156]	342	102[78;137]	0.68

Table 4.2: results according to BE

Gold Standard: Apgar5					
	#	DISEASED	#	HEALTHY	P value
Mean NN	15	472[447;492]	358	457[434;490]	0.39
SD NN	15	97[75;111]	358	79[59;103]	0.10
VLF power (bpm ²)	15	23479[10984;3926]	358	21269[13038;34148]	0.95
LF power (bpm ²)	15	1578[725;2681]	358	1670[977;2532]	0.88
HF power (bpm ²)	15	15[12;20]	358	15[10;25]	0.96
LF/HF ratio	15	118[72;135]	358	101[68;157]	0.96
TINN	15	141[82;180]	358	102[70;139]	0.14

Table 4.3: results according to Apgar5

4.4 Discussion

In the present thesis endeavor, percentiles emerged as a potent and invaluable statistical tool, wielded with precision to illuminate the intricate distribution patterns of neonatal data concerning three pivotal diagnostic features: pH, base excess (BE), and the Apgar score at 5 minutes (Apgar5). Employing percentiles facilitated the systematic segmentation of the neonatal dataset into distinct categories predicated on the varying values of these diagnostic features, thereby laying bare nuanced trends and variations that permeate the entire dataset.

In tandem with percentile analysis, the diligent computation of p-values was undertaken to meticulously gauge the statistical significance of disparities observed between cohorts of healthy and pathological neonates, within the purview of each individual diagnostic feature. These calculated p-values assumed a pivotal role as a statistical yardstick, enabling the objective determination of whether the observed dissimilarities in the distributions of diagnostic features could be attributed to statistical chance or indeed possessed substantial statistical significance.

The utilization of percentiles in our analytical framework conferred several notable strengths. First and foremost, it provided an accessible and intuitive means of comprehending the underlying data distribution. In so doing, it unveiled key summary statistics such as medians and quartiles, furnishing the groundwork for a robust and comprehensive assessment of how the diagnostic feature values permeate the neonatal population. Consequently, this facilitated the discernment of inherent patterns, identification of potential outliers, and an elucidation of the dynamic interplay of feature values among neonates.

Furthermore, the incorporation of p-values served to elevate the methodological rigor of our investigative approach. These p-values, derived through rigorous statistical testing, offered a quantifiable metric for assessing the statistical significance of disparities. This vital addition fortified the analytical framework, ensuring that the conclusions drawn were grounded in a bedrock of compelling statistical evidence.

However, it is incumbent upon us to acknowledge the limitations inherent in the employment of percentiles and p-values. While percentiles are invaluable in delineating data distribution, they may not furnish a holistic comprehension of the intricate relationships that underlie diagnostic features and neonatal health. Additionally, the interpretation of p-values is contingent upon the assumptions

of the statistical tests employed, and the determination of significance may exhibit variability contingent upon the chosen significance threshold.

Armed with the tools of percentiles and p-values, our research endeavors bore fruit, unveiling discernible disparities in the distributions of pH, BE, and Apgar5 between cohorts of healthy and pathological neonates. Notably, our meticulous scrutiny of the data tables revealed that, with regard to Apgar5, none of the features exhibited statistically significant differences ($p > 0.05$).

In the case of BE and pH, a more nuanced picture emerged. Some features exhibited statistically significant disparities, exemplified by the Standard Deviation of NN intervals. Conversely, other features, such as TINN of BE and pH, failed to meet the threshold for statistical significance, as evidenced by p-values exceeding 0.05. It is noteworthy, however, that in the case of BE, the p-value associated with VLF power hovered at 0.05, straddling the boundary of statistical significance and non-significance, ultimately being excluded from further consideration as a result of its tenuous standing.

CONCLUSIONS

This thesis endeavor was dedicated to the identification of the most discerning parameter among pH, base excess (BE), and Apgar score at 5 minutes (Apgar5) for the precise diagnosis of neonatal hypoxia.

The results unveiled a noteworthy limitation associated with the efficacy of Apgar5 as a standalone diagnostic tool in the context of neonatal identification, indicating relatively diminished performance. It is plausible that the removal of NaN (Not a Number) values within the dataset, undertaken not only at its initiation but also intermittently during its progression, may have contributed to these outcomes. Notably, a pronounced disparity was observed between healthy and afflicted neonates, exemplified by a substantial difference in the case of BE, where 53 neonates contrasted with 342 affected neonates.

This thesis underscores the inherent advantages of employing objective parameters in distinguishing between neonates with pathological conditions and those without. Conversely, subjective parameters, exemplified by Apgar5, may not serve as primary diagnostic indicators but rather function as indicators of suspicion, necessitating further diagnostic assessments for confirmation or exclusion of pathology.

Concerning the analysis of specific features, further comprehensive investigations are warranted to ascertain whether the computation of standard deviations of NN intervals in isolation can serve as a viable substitute for the assessment of pH levels in neonates.

In summation, it is unequivocally evident that pH levels emerge as the paramount and precision-driven diagnostic parameter for neonatal hypoxia. Our rigorous data analysis consistently reaffirms the significance of pH in effectively distinguishing between healthy and pathological neonates, thereby cementing its status as a robust diagnostic indicator with practical implications in clinical settings.

Nevertheless, in instances where alternative parameters such as Apgar5 are contemplated, we advocate for a judicious approach. The imperative for repeated testing, preferably conducted two or three times with subsequent averaging of results, becomes indispensable to ensure the reliability and accuracy of such measurements. This additional step serves to mitigate potential variability and mitigate the risk of misinterpretation.

Furthermore, we underscore the pivotal importance of meticulous database management. The presence of numerous NaN values within the dataset bears the potential to engender misconceptions and compromise the integrity of our findings. Therefore, the implementation of comprehensive data validation and quality control measures remains an imperative to fortify the foundations upon which our analyses rest.

In conclusion, our methodology, notably enriched by the utilization of p-values, effectively bridges the chasm between theoretical constructs and practical application, augmenting the robustness of our diagnostic approach. However, it is incumbent upon us to exercise prudence, accord primacy to pH levels as the foremost diagnostic parameter, and adhere rigorously to testing protocols when contemplating alternative measures. Our unwavering commitment to the principles of data integrity and methodological precision propels us forward in our quest to advance the realm of neonatal healthcare and continue to provide invaluable insights for the enhancement of clinical practice.

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