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Long-term Bioeffects of Prenatal Doppler Ultrasound Exposure and the Relation to Genetic Defects of the Fetus in Utero

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Abstract

Cardiotocography, fetal heart rate contraction recording, refers to a method for the simultaneous registration and recording of the heart rate of the unborn child and the uterine contractions in the expectant mother. The procedure is used both in pregnancy care and during labor. The fetal heart rate is usually determined using *pulsed-wave Doppler ultrasound* and recorded in beats per minute. The mother's uterine contractions are simultaneously recorded using a separate uterine contraction sensor, a pressure gauge. There are two methods for this: the rarely used intrauterine direct pressure measurement, which can only be used after the amniotic sac has opened, i.e., during labor, and the more common external pressure measurement using a tocodynamometer. This differential pressure gauge responds to changes in abdominal tension during a contraction, leading to large individual fluctuations in the recording of uterine contractions. The interpretation of a CTG or the calibration of the device must therefore take into account the constitution of the pregnant woman and her reports of the palpability of contractions. The course of changes in the fetal heart rate is interpreted taking into account the uterine contractions and the gestational age in pregnancy care or the progress of labor. In cases of suspected inadequate fetal oxygenation and uteroplacental dysfunction, a contraction stress test with CTG monitoring can be performed. It has many false-positive results and is no longer recommended in the current S3 guideline for vaginal delivery from 2022 and could have pathological influence developing autism spectrum disorder in childhood. Recent studies hypothesis that intermittent fetal heart rate contraction recording could have influence on genetical architecture structure of the fetus in utero.

Keywords: Cardiotocography; Pregnancy; Fetus; Genetics; Autism

Introduction

The inventor of cardiotocography, the German gynecologist Konrad Hammacher, developed a risk assessment system, Hammacher Score, based on his findings, which proved to be impractical for obstetric practice. The German perinatal physician Wolfgang M. Fischer (1932–2007) presented a simplified variant of Hammacher's evaluation system in 1976, known as the Fischer Score, primarily intended for pregnancy. Subsequently, the International Federation of Gynecology and Obstetrics (FIGO) introduced another relatively simple scoring system that quickly gained acceptance. All three evaluation systems are still in international use, with terminologies sometimes being mixed. The S3 guideline for German-speaking countries recommends using the FIGO Score. A cardiotocograph records contractions and heart rate. The device shows the charger with trays for 3 wireless sensors.

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Soon after the invention of the stethoscope by René Laennec (1781–1863), attempts were made to apply this invention in obstetrics. Initially, the focus was on proving the unborn child's viability. Another French physician, Adolphe Pinard (1844–1934), designed a wooden stethoscope specifically for obstetrics ("Pinard tube") towards the end of the 19th century, which is still used in obstetric monitoring today. However, a significant drawback is that it is not practical for continuous monitoring of fetal heart activity. In 1944, Arthur Weber conducted fundamental work on heart sound recording. In 1964, the German gynecologist Konrad Hammacher (1928–2001) developed the first cardiotocograph, a recording device for fetal heart activity, enabling continuous monitoring of fetal well-being. Initially, the heart rate was determined phonocardiographically, i.e., by deriving heart sounds using a microphone. Other approaches involved deriving the fetal electrocardiogram in different ways to determine the heart rate. *Since the late 1960s, the ultrasound Doppler method has been used*. Ultrasound is sent from a probe placed on the mother's abdomen, reflected by the fetal heart, and received back. The fetal heart rate is determined based on the Doppler effect (frequency deviation of the received signal due to the movement of the reflecting heart). Phonocardiotocography, ultrasonocardiotocography, and fetal electrocardiotocography are now possible in conjunction with simultaneous uterine contraction registration. The measurement of uterine contractions dates back to the description of a tocodynamometer in 1957, which has a fixed outer ring and a movable detector plate with a force sensor to determine the "impression force." The principle has been modified to compensate for interference.

For determining the optimal delivery time for pregnant women with small or sick children, physiologist Geoffrey Sharman Dawes (1918–1996) and obstetrician Chris Redman (born 1941) developed the Oxford CTG (also known as Computer CTG, cCTG) through decades of work. It features integrated software in the recording device that allows for a much finer analysis of fetal heart activity. This enables the detection of subtle changes indicating fetal endangerment in utero, such as due to preeclampsia or fetal growth restriction. The short-term variation (STV) has proven to be a valuable new parameter, especially the variation in the average absolute time difference between consecutive heartbeats. However, the cCTG plays a minor role in obstetrics and is not recommended in the current S3 guideline. Today, CTG devices commonly used in delivery rooms (Kineto-CTG) record fetal heart rate, maternal uterine contractions, and fetal movements. These movements provide additional information about the baby's condition. Fetal movements can be detected using the same ultrasound sensor that measures heart activity. Data transmission in these devices is usually wireless from battery-powered transducers on the mother's abdomen to the recording unit. This allows the mother to move freely while monitoring the baby's condition. The adjacent photo shows such a CTG. Ultrasound scanning has been a standard diagnostic and screening tool in obstetrics for over 50 years. B mode ultrasound has not shown any immediate or long-term harm to fetuses. However, the increasing use of high levels of Doppler ultrasound during early development raises concerns about its safety. Studies have shown that exposure to Doppler ultrasound in utero can lead to increased cell death in animal models and long-lasting effects, such as increased non-right-handedness in humans. There is a possibility of developmental implications for fetuses exposed to Doppler ultrasound early in pregnancy, possibly due to thermal or mechanical disruption causing free radical damage. Excessive free radical exposure in early gestation could be a key factor in developmental programming effects. This raises concerns about the potential risks for fetuses exposed to high levels of ultrasound. More research, including animal studies and observational data collection, is needed to better understand the long-term effects of Doppler ultrasound exposure. In the meantime, it is advisable to follow the principle of keeping exposure levels 'as low as reasonably achievable' (ALARA) when using Doppler ultrasound on first-trimester fetuses.

Effects of long-term application of pulsed-wave Doppler ultrasound

Doppler ultrasonography (DUSG) is commonly used for fetal assessments. Recent interest has focused on assessing the heating effects of diagnostic ultrasound in clinical settings. Recent studies aimed to evaluate the in vivo effects of ultrasound exposure of varying durations of 10 to 20 minutes using common imaging systems. Liver tissue shows to be a significant increase in lipid peroxidation (TBARS) in Doppler applications. B-mode ultrasound was found to be safer for fetal tissue due to lower temperature rise compared to Doppler. Antioxidant enzyme activity increased in both B-mode and Doppler groups as a protective response. In brain tissue, lipid peroxidation slightly increased in B-mode doppler sonography, likely due to the brain's lipid concentration. Antioxidant enzyme activity and lipid peroxidation significantly seems to increase in Doppler applications in both liver and brain tissues, indicating potential harmful effects from temperature rises (5).

Neurosonography is widely used to visualize the developing brain and spinal cord in fetuses, infants, and children. The rapid cell turnover during brain development makes it susceptible to genetic mutations from external stimuli. There is a lack of human clinical studies on the long-term effects of postnatal ultrasound exposure on the central nervous system. Current research on prenatal and postnatal ultrasound use is inconclusive about safety. Adhering to standardized examination protocols and patient handling guidelines can reduce the risk of adverse outcomes in neurosonography. Following the ALARA principle and implementing safety measures can help minimize potential risks in neurosonography. A recent study examined the

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impact of new-generation Doppler ultrasound at varying frequencies during pregnancy on postnatal renal development (2). Six pregnant rats were divided into three groups. The first group served as the control with no intervention. The second group received daily 15-minute transabdominal DUSG from gestation to birth, while the third group received DUSG every two days (2). After 60 days, 24 male pups were sacrificed for renal tissue analysis (2). Results showed increased levels of malondialdehyde, glutathione, urea, Ca, K, and Cl in the DUSG groups compared to the control group. Histopathological analysis revealed increased tubular damage in the DUSG groups (2). Immunohistochemical evaluation showed higher Caspase-3 expression in the DUSG groups. Although superficial areas of tubules increased in the DUSG groups, the difference was not significant. Multiple exposures to new-generation DUSG during pregnancy had adverse effects on postnatal renal tissue development, suggesting the need for minimal exposure and avoidance of re-exposure. Furthermore, only few studies exist analyzing multiple DUSG exposure during pregnancy and genetic gene alterations in these babies (1-8). Future research in this important aspect should closer evaluate a significant association between DUSG exposure and influence on genetic architecture in a fetus.

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