Effects of maternal obesity on electrophysiological characteristics of the fetal heart and perinatal events

Ph. D. dissertation thesis

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Pécs, 2023.

UNIVERSITY OF PÉCS, FACULTY OF HEALTH SCIENCES

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Introduction

Obesity is growing at epidemic proportions worldwide, affecting both adults and children, with prevalence rates doubling in 70 countries since the 1980s [1] and almost tripling since 1975 for the world's total population. Obesity has been declared a public health problem by the American Medical Association (AMA) and the World Health Organization (WHO) has called it the greatest health challenge of the 21st century. Obesity affects both mental and physical health and, in association with other diseases, increases mortality and morbidity, such as hypertension, dyslipidaemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnoea, respiratory diseases and malignant tumours. There is a number of statistical evidence to show that morbid obesity is the most common health problem affecting women of reproductive age [2].

Definition of obesity

The two easiest ways to measure body size are weight and height. Five decades ago, Ancel Keys and colleagues, after examining a number of characteristics, found that the body fat content correlated most closely with the body shape characteristic described by the ratio of body weight to height squared (BMI). This has remained the most widely used body type characteristic ever since. Large-scale population studies have then further refined the observations by standardizing BMI as a function of age in children, adolescents and the adult population [8]. Based on these, we speak of overweight for BMIs above 25 kg/m^2 and obesity for BMIs above 30 kg/m^2 (Table 1). According to a recent study 32% of adult women and 28% of adult men in Hungary are obese. According to the 2014 survey of the National Institute of Pharmacy and Food Hygiene (OGYÉI), the average BMI of the adult Hungarian population in 2014 was 27.4 kg/m^2, can be therefore considered overweight.

Table 1. *Relationship between body type and BMI*

body type	lean	normal	overweight	obesity		
				mild (I.)	moderate (II.)	severe (III.)
BMI $(kg/m)^2$	<18,5	18,5-24,9	25-29,9	30-34,9	35-39,9	≥40

The health significance of obesity and its implications for obstetrics

Such a high rate of obesity is even more alarming given that more than four million people die from obesity-related complications worldwide each year, with two-thirds of deaths attributed to cardiovascular disease. The average body mass index for women of reproductive age increased from 22.1 (21.7-22.5) in 1975 to 24.4 (24.2-24.6) in 2014. And the prevalence of obesity (BMI>30kg/m^2) doubled. Morbid obesity during pregnancy can have both short- and long-term adverse consequences for the mother and the foetus [3]. It can even make pregnancy more difficult and increase the risk of miscarriage in early pregnancy. Abnormal obesity affects the hypothalamic-pituitary-ovarian axis, which can lead to disruption of the sexual cycle. The corpus luteum phase is shortened and FSH, LH, progesterone concentrations are lower. In addition, it causes changes in the function of the granulosa cells of the ovaries and the composition of the follicular fluid surrounding the oocytes. Obesity can then lead to impaired follicular maturation through a number of factors. Obese women are more likely to have pregnancy-related conditions such as gestational diabetes, preeclampsia, infections, thrombosis, postterm pregnancy, more frequent need of induction of labour and a higher incidence of caesarean section. Similarly, morbid obese pregnant women are more likely to have preterm birth, stillbirth, various malformations, macrosomia, excessive fetal weight gain leading to birth injuries, and a higher rate of juvenile obesity in their children. Obese patients are more likely to have anaesthetic complications and may also have a higher incidence of impaired wound healing after surgery. Fetal overweight (macrosomy) is defined as a fetus with an estimated fetal weight of more than 4000 g or in the upper 10% of the percentile for the proper gestational age. In addition to genetic factors, maternal diabetes and obesity are the main causes. The maternal circulation undergoes dramatic physiological changes during pregnancy. Compared to the pre-pregnancy state, a significant decrease in systemic vascular resistance (30-70%) causes intravascular fluid retention and an increase in serum plasma volume, leading to a decrease in haematocrit and plasma osmolality [4]. Increases in pulse volume and heart rate lead to an increase in pericardial volume, which peaks in the second trimester and remains at this value until delivery.

Assesment of fetal weel-being

The fundamental aim of in utero fetal monitoring is to improve perinatal outcomes, particularly by reducing the incidence of stillbirth and long-term neurological damage. Fetal damage is caused in the vast majority of cases by hypoxia and acidosis. Intrauterine diagnostic

methods are based on the premise that fetuses whose oxygenation in utero is disturbed respond to this situation with detectable physiological signs of adaptation or decompensation.

Cardiotocography (CTG)

There are basically two electrical ways to monitor the fetal heart rate. Firstly, by detecting the electrical signals of the heart by means of an electrode attached to the skin of the fetus via direct fetal conduction, or more commonly, by detecting Doppler ultrasound signals indirectly through the abdominal wall of the mother. Continuous fetal heart rate monitoring based on cardiotocography has allowed real-time monitoring of fetuses during labour, giving obstetricians and midwives the opportunity to react in time to changes in fetal heart rate before hypoxic ischaemic damage occurs. Despite the fact that CTG was developed as a screening tool to predict fetal hypoxia, its positive predictive value from this perspective is only around 30%. With the accumulation of experience, continuous improvements have resulted in new recommendations for the practical interpretation of various CTG anomalies, but the rate of false positive CTG tests remains very high (around 60%).

Auscultation

Until the development of cardiotocographs, stethoscopic fetal heartbeat detection was the only method of assessing the intrauterine condition of fetuses. With the appearence of CTGs, it was quickly superseded in clinical practice. In recent years, it has a renaissance, with studies showing that than CTG monitoring in low-risk pregnants is no safer, than intermittent auscultation and continuous CTG monitoring increases the number of medical interventions during labour that do not have significant benefits.

Ultrasound examination

In addition to the assessment of the amount of amniotic fluid, it is important information to assess the movements and muscle tone of the fetus, and in addition to this, a cardiotocographic examination of the foetus provides a proper biophysical profile, which has a false negative value of 0.8/1000 according to a large comparative study, although the false positive rate is high (60%). The disadvantage of US is that the ultrasound equipments are expensive and vulnerable. The proper performance of the scans requires practice and their intrapartum usage is cumbersome, given that the fetal status in the birth canal is problematic due to "shadowing" by the pelvic bones and reduced compliance of the mother who is in active labour.

Fetal (scalp) blood sampling

Currently, the only recognised objective fetal condition diagnostic method that provides accurate information of the in-utero condition of fetuses is the fetal scalp sampling and pH determination method developed by Sahling in 1972. It is an invasive test which is painful for the mother, involves a risk of infection for the fetus despite adequate sterility and this limits the usefulness of the method. It is not suitable for continuous monitoring, only provides a snapshot and may be affected by venous stasis in the caput succedaneum (fetal skull) during labour.

Fetal pulse oximetry

Photoabsorption oxygen saturation measurement. Similar to scalp blood sampling, it can be used for fetuses in the cephalic position after rupture of the membranes with at least 3 cm of cervical dilatation. It allows continuous recording, but the attached sensor is not fixed, so it is easily dislocated, interrupting recording periodically and increasing the risk of infection with each repositioning. In addition, the devices are very expensive, which limits their widespread use, and statistics show that their usage does not significantly reduce caesarean section rates.

Fetal ECG examination, the STAN method

Developed over the last decades, this test combines the features of continuous CTG monitoring and morphological analysis of the fetal ECG ST segment. The method is based on the principle that, in the presence of reduced oxygenation, the fetal myocardium switches to anaerobic metabolism. This process causes a change in the electrophysiological characteristics of the fetal heart, which is visible on the electrocardiogram. The T wave, which represents

repolarization, and the morphology of the ST segment also change. These changes have been observed to precede hypoxic tissue damage by hours (Figure 1).

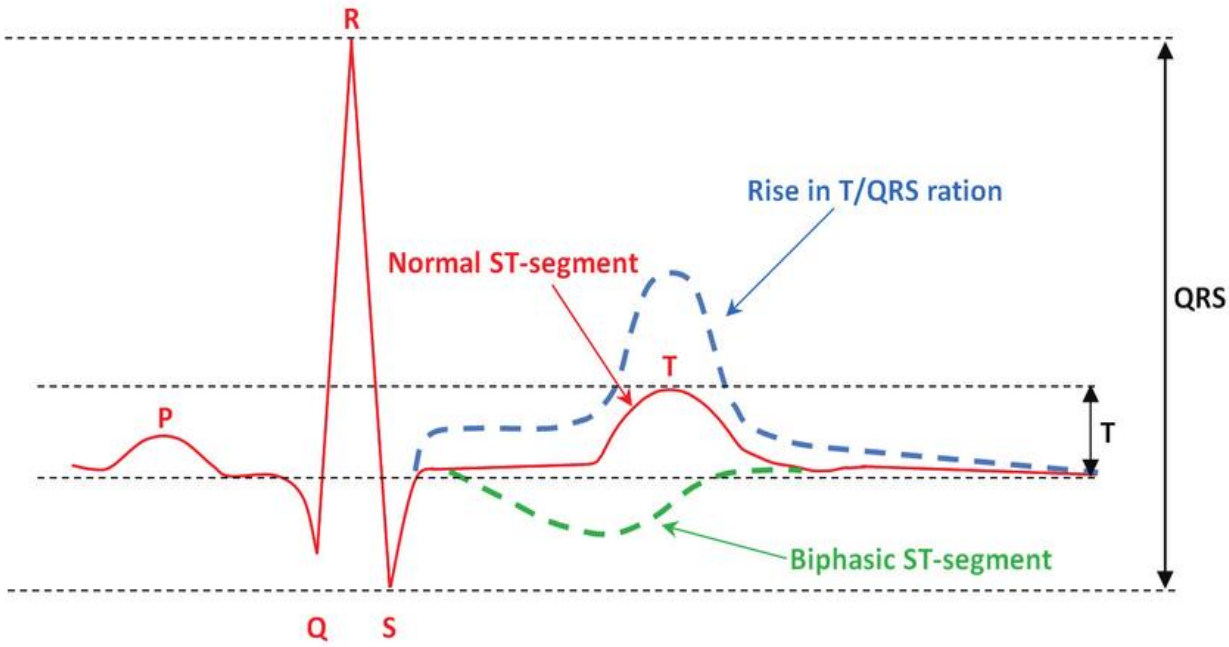

Figure 1: ECG changes in response to hypoxia; Martinek, Radek & Žídek, Jan. (2012) A System for Improving the Diagnostic Quality of Fetal Electrocardiogram. Przeglad Elektrotechniczny

Between 1984 and 2004, Rosen et al. concluded, after several experiments, that acute hypoxaemia causes the fetus to respond with ST elevation and a progressive increase in T wave amplitude, quantified by the ratio of T wave to QRS complex amplitude (T/QRS ratio) [5]. This process is accompanied by the release of catecholamines, which is associated with the activation of myocardial ß-receptors. The elevated T/QRS ratio indicates a physiological adaptation of the fetal heart to hypoxia by increasing glycogenolysis and myocardial performance. Their observations showed that in fetuses where intrauterine infection, severe fetal anaemia, hypotension were detected, in utero necrosis was preceded by a steadily rising ST elevation. This observation led to the development of a direct fetal monitor system that automatically analyses T wave height in relation to the amplitude of the QRS complex. The direct fetal monitor system allows us to detect the transition as the fetus switches from aerobic to anaerobic metabolism. A weakness of the STAN method is that the fetal heart generates a much weaker electrical signal than the maternal heart, by up to 80-100 times. When the method was first

developed in the early 2000s, detection of this was only possible by direct fetal wiring, which required the insertion of a coiled electrode directly into the fetal skin.

Our study

As pregnancy, obesity has also a well-known effect on circulation. Abnormal obesity can alter cardiac morphology and may be the source of many ECG anomalies. Given that abnormal obesity can hold a number of problems from both obstetric and maternal and fetal haemodynamic perspectives, the aim of our study was to compare intrapartum circulatory parameters and obstetrical outcomes in obese and normal weight womens. In addition, we investigated whether fetal ECG abnormalities during delivery are detectable in obese patients and, if so, whether they are more frequent than in normal-weight pregnant women. We used continuous, real-time fetal ECG analysis to investigate the effect of maternal circulatory overload due to pregnancy and/or morbid obesity on fetal circulation in otherwise low-risk pregnant women.

Our prospective study was conducted at the Universitiy of Pécs at the Department of Obstetrics and Gynaecology between 1 January 2013 and 1 January 2014. For our investigation, we selected 168 low-risk pregnant women from 2840 patients who gave birth at our institution during the study period. The samples were collected consecutively. In low-risk singleton pregnants in active labour who were at least at 36 weeks of gestation and agreed to continuous direct fetal registration, we started STAN monitoring after rupture of membranes in fetuses in the cephalic position. We excluded pregnant women who had a history of infection (HIV, HSV, Hepatitis), fetal coagulopathy, fetal blood loss (e.g. due to partial placental abruption) or who arrived in the expulsion phase. In addition, all cases where STAN monitoring was not applicable (placenta previa, vasa previa) were excluded. The study population was divided into two groups based on BMI. The obese group consisted of women who gave birth in our clinic (n=60) and had a BMI above 30 kg/m^2 on the day of delivery, and the control group consisted of women (n=108) with a BMI below 30 kg/m^2 at the onset of delivery. Both populations consisted of low-risk, pathology free pregnant women who delivered their babies in our institution without serious complications during the study period. There were no differences between the two groups in maternal age or gestational weeks at delivery, and no ethnic or significant parity differences. We recorded the mode of delivery, the method of anaesthesia during labour, the dose requirements of epidural anaesthesia (ropivacaine and fentanyl*)* if used. In addition, we documented the duration of scalp electrode monitoring during the first and second stages of labour, birth injuries, amount of blood loss during delivery, neonatal birth weight, neonatal

APGAR scores at 1' and 5' minutes, and the proportion of neonates requiring intensive care. For fetal status assessment we used STAN® (SR 31 model, Neoventa Medical, Gothenburg, Sweden) in addition to conventional cardiotocography (CTG), which provides earlier detection of preventable fetal damage and thus more time to perform the necessary interventions. Blood samples for monitoring acid-base status were obtained from the clamped umbilical artery and vein immediately after delivery. Samples were analysed with a blood gas analyser (GEM 3500 Premier, Instrumentation Laboratory) by calculating the base deficit using the Siggard-Andersen algorythm.

Statistical analyses including Mann-Whitney and Kolomgorov-Smirnov and Chi-square tests were performed using IBM SPSS Statistics 2.0 software at the Institute of Bioanalytics, University of Pécs. Results are reported in mean ± standard error of mean (SEM) format.
The significance level was set at $p < 0.05$.

Our results

A significant difference in the spontaneous delivery rate was found between the obesity group (75%, 45/60) and the control group (88.89%, 96/108). The obesity group had a 5% (3/60) rate of vacuum extraction, whereas the control group had no operative delivery (Table 2).

Table 2 Aggregate obstetric outcomes

	Obez	**Control**
P.v.n. birth rate (%)	75	88.89
Percentage of operative delivery (%)	5	0
Caesarean section rate (%)	20	11.1
Episiotomy rate (%)	81.25	74.22
Rate of perineal injuries (%)	31.25	12.54
Rate of epidural anaesthesia (%)	90	63.04

The mean birth weight of the fetuses was 3220 g (± 270 g) in the normal maternal body weight group and 3412.5 g (± 229.8323664 g) in the obese group. A difference in the caesarean

section rate was also observed between the groups, although it was not significant (p=0.08). Episiotomy was performed in 81.25% (39/48) of vaginal deliveries in the obesity group. The proportion of first or second degree perineal injuries that occurred spontaneously (40%) or with a episiotomy (60%) was 31.25% (15/48). In the control group, the rate of episiotomy was 74.22% (71/96) and the rate of perineal injuries was 12.54% (12/96), which occured beside episiotomy in 8.7% (6/96) of cases. In the obese group 85% (51/60) of the women in labour used epidural anaesthesia, compared to 60% (65/108) in the control group.

Neonatal outcome

No statistically significant differences were found in the base neonatal parameters between the groups studied. All newborns were born in good general condition with satisfactory adaptation. No newborn in any group developed definitive metabolic acidosis.

ST events

The mean direct total registration time was longer in the obesity group (276.08 ± 39.80 min vs 184 ± 21.50 min, $p < 0.05$), due to longer dilation stage (263 ± 39.82 min vs 171.82 ± 21.54 min, $p < 0.05$). No significant difference was found in the duration of the second stage of labour between the two study groups (13.8 ± 3.49 min vs 12.18 ± 1.41 min).

Summary

In our study, we compared intrapartum fetal ECG abnormalities and neonatal outcome in low-risk obese and normal weight patients. We found an increase in the rate of emergency caesarean sections in the obese group, although the difference was not significant. In addition, this group had a significantly lower rate of spontaneous vaginal deliveries.

Previous studies have shown a higher rate of emergency caesarean sections among obese pregnant women [6]. There are several theories to explain this. The reduced uterine activity may lead to prolonged dilatation phase, obstructed labour and it is associated with a higher rate of hypercholesterolaemia that can be detected in obese patients. Cholesterol plays an important role in smooth muscle contraction [7]. Higher blood cholesterol concentrations reduce the viscosity/permeability of cell membranes and the influx of calcium ions during smooth muscle contraction, leading to a decrease in contractility. On the other hand, obese women have higher blood concentrations of leptin, a hormone produced by adipose tissue with metabolic and appetite-enhancing effects. Studies have shown that leptin reduces the contractility of the myometrium [8]. Finally, adipose tissue accumulation in the pelvic cavity of the pregnant woman and in the birth canal may also play a role and may constitute an obstetric obstacle.

In our study, we primarily sought to determine whether differences in the electrophysiological characteristics of the intrapartum fetal ECG, and more specifically the ST segment could be observed in low-risk normal weight and obese fetuses. Our hypothesis is that the overloaded circulation in pregnant women with morbid obesity, caused by both obesity itself and pregnancy, will have a significant impact on feto-placental circulation, resulting in significant electrophysiological abnormalities on the fetal ECG and worsen the neonatal outcome. Our results have shown that obesity alone, as an independent risk factor, does not have a dramatic effect on the fetal ECG. Further studies with larger numbers of cases are needed to confirm this. For the control group, we observed some non-significant increase in baseline T/QRS ratio (>0.05; >10min): however, in our experience, this had neither an objective (umbilical artery blood gas analysis) nor a subjective (0-5-10min APGAR) effect on neonatal outcome.

In conclusion, fetal heart frequence monitoring augmented by continuous fetal ECG detection is a useful and reliable way to monitor the intrauterine fetal status during delivery.

Possibilities for the future

Electronic fetal monitoring has a key role in obstetric care for almost five decades. Despite all efforts, the most widely used devices continue to be based on visual interpretation of the pattern of fetal heart rate changes. These tools, although they have brought dramatic improvements in perinatal morbidity and mortality, have failed to significantly reduce the incidence of some ante- or intrapartum event-related conditions (e.g. cerebral palsy). Moreover, the high degree of subjectivity in the evaluation of the study was reflected in the lack of specificity of the methods. Fetal ECG analysis holds great promise. The advent of the STAN method has generated a worldwide response, with a number of convincing clinical studies to support its efficacy, but its invasiveness and cost have dampened initial enthusiasm. Researchers see the clinical success and business failure of STAN in the fact that the way to increase the accuracy of monitoring is through analysis of fetal ECG changes, but a device based on such a method must be non-invasive. Despite all the improvements, it seems that the detection of fetal heart rate changes will remain the basis of fetal status diagnostics for some time to come. So far, no newly developed device has been able to displace conventional cardiotocography in everyday obstetric care. Reflecting this fact, the International Federation of Obstetrics and Gynaecology (FIGO) published in 2015 a consensus-based professional recommendation (Table 3) on the use of cardiotocography and the interpretation of registries. It has done this to standardise the interpretation of the patterns of different heart rate anomalies and to assist healthcare professionals [9].

Table 3 FIGO (2015) recommendation for the evaluation of CTG findings

	Normal CTG	**Suspicious CTG**	**Abnormal CTG**
Base frequency	110-160 bpm	Absence of at least one physiological characteristic without abnormal pattern	<100 bpm
Variability	5-25 bpm		Reduced/increased variability;sinusoidal pattern
Decelerations	No repetition		Repeated or prolonged late decelerations >30 min (or >20 min in case of reduced variability); >5 min deceleration
Evaluation	Hypoxia/acidosis none	Low probability of hypoxia/acidosis	High likelihood of hypoxia/acidosis
suggested intervention	no intervention necessary	interventions to improve fetal oxygenation; additional tests; continous monitoring	Immediate intervention to improve fetal oxygenation; facilitation of delivery; termination of delivery in acute situation

Acknowledgements

This study was made possible by the project "Improving the success of in vitro fertilization by non-invasive methods" J.B. (SROP-4.2.2.D-15/1/KONV-2015-0004). We thank the staff, doctors, nurses and midwives of the Department of Obstetrics and Gynaecology and the Department of Neonatology of the University of Pécs who worked with us in the delivery room. We would also like to thank Professor Dr. Tibor Ertl and Professor Dr. Lajos Bogár for their support and useful advice and suggestions.

Summary of new results

- No significant difference was found in the rate of caesarean sections between obese and normal patients in the study population

- Operative termination of labour (caesarean section, vacuum extraction) was more common in obese pregnant women
- In both groups, the newborns were born in good all-cause condition, and no fetal acidosis was found in any of the newborns (5-minute Apgar values = 9.67 ± 0.07 and 9.86 ± 0.06, respectively; pH in the umbilical cord = 7.29 ± 0.02 and 7.21 ± 0.01, respectively).
- The prevalence of macrosome fetuses was higher among obese mothers, but the difference was not significant
- Perineal injuries were more common in obese pregnant women
- On average, longer recording times were measured in the obese group as a result of the longer dilatation phase, but no significant differences were found in the observed fetal ECG abnormalities and ST events between the groups
- Based on our studies, we came to the preliminary conclusion that obesity affects obstetric outcome but does not disturb the electrophysiological characteristics of the fetal heart.
- More case studies are needed to confirm our results

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