UNIVERSITY OF PRIMORSKA
FACULTY OF MATHEMATICS, NATURAL SCIENCES
AND INFORMATION TECHNOLOGIES

Iva Šklempe Kokić

# THE IMPACT OF STRUCTURED AEROBIC AND RESISTANCE EXERCISE ON THE COURSE AND OUTCOME OF GESTATIONAL DIABETES MELLITUS

# VPLIV STRUKTURIRANE AEROBNE VADBE IN VADBE MOČI NA POTEK IN IZID NOSEČNIŠKE SLADKORNE BOLEZNI

Doctoral thesis

Izola, September 2016

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APPLIED KINESIOLOGY

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Doctoral thesis

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Izola, September 2016

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Ključne besede: nosečnost, diabetes mellitus, terapevtska vadba, trening, gibalna aktivnost, glikemična kontrola

Povzetek: Nosečniška sladkorna bolezen (NSB) je definirana kot kakršnakoli intoleranca na ogljikove hidrate, ki je prvič diagnosticirana v času nosečnosti (Metzger idr., 2007). Povezana je s številnimi neželenimi izidi, tako za mater, kakor za plod. Predmet doktorske disertacije je bil preučiti vpliv strukturiranega vadbenega programa, sestavljenega iz vaj za vzdržljivost in proti uporu, na potek in izid NSB. Cilj raziskave je bil raziskati kako omenjeni program vpliva na parametre glikemične kontrole, število zapletov v nosečnosti, med popdaki in porodom, porast telesne mase in maščobne mase v nosečnosti ter na parametre novorojenčkov. Osemintrideset nosečnic smo naključno razporedili v dve skupini: eksperimentalno (ES), kjer je potekala obravnava z vadbeno in medicinsko prehransko terapijo (ES; N = 18) in kontrolno (KS), ki je bila obravnavana zgolj z medicinsko prehransko terapijo (KS; N = 20). Strukturiran vadbeni program je bil izvajan od trenutka diagnoze bolezni do zaključka nosečnosti, dvakrat tedensko po 50–55 minut. Poleg tega so nosečnice v ES izvajale še najmanj 30 minut hitre hoje dnevno. V času študije, je bilo izvedenih skupno 365 vadbenih ur, z 20.28 ± 7.68 vadbenih ur povprečno na posamezno preiskovanko in upoštevanje protokola je bilo 84.22%. Vadbeni program ni imel nobenih neželenih stranskih učinkov. Rezultati kažejo statistično pomembno razliko v ravni postprandialne glukoze ob koncu nosečnosti ($P < 0.001$). Med skupinama ni bilo statistično pomembnih razlik v ravneh glukoze merjene na tešče ob koncu nosečnosti, v stopnji zapletov v nosečnosti, med popadki in porodom, v telesni teži, odstotku telesne maščobe in porastom telesne mase v določenih časovnih točkah med nosečnostjo, pri Apgarjevem testu novorojenčka, v njegovi telesni masi in ponderalnom indeksu. Statistično pomembne razlike so bile v indeksu telesne mase novorojenčkov, ki je bil nekoliko višji v eksperimentalni skupini ($P = 0.035$). Rezultati naše študije jasno potrjujejo

pozitiven učinek vadbe na raven glukoze v krvi postprandijalno ob koncu nosečnosti. Prav tako, se je vadba, kot dodatna terapija pri obravnavi NSB, izkazala za popolnoma varno. Terapevtska vadba med nosečnostjo je lahko učinkovita in varna metoda za zdravljenje NSB, skupaj z drugimi ukrepi življenjskega sloga.

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Key words: pregnancy, therapeutic exercise, training, physical activity, glycaemic control

Abstract: Gestational diabetes mellitus is defined as any carbohydrate intolerance first diagnosed during pregnancy (Metzger et al, 2007). It is associated with a variety of adverse outcomes, both for the mother and fetus. The objective of this thesis was to examine the effects of structured programme consisting of aerobic and resistance exercises on the course and outcomes of gestational diabetes mellitus. Aim of research was to investigate how this exercise programme affects parameters of glycaemic control, rate of complications in pregnancy and during labour and delivery, weight gain and fat mass gain in pregnancy, and newborn's parameters. Thirty-eight pregnant women were randomly assigned into two groups: experimental group treated with exercise therapy and medical nutritional therapy (EG; N = 18) and control group (CG; N = 20) treated with medical nutritional therapy alone. Structured exercise programme was performed from the diagnosis till the end of pregnancy two times per week for the duration of 50-55 minutes. Furthermore, pregnant women in EG performed at least 30 minutes of vigorous walk once per day. A total of 365 exercise sessions were performed during the trial, with 20,28 ± 7,68 sessions on average per subject and adherence to protocol was 84,22%. There were no adverse side effects caused by the exercise programme. Results showed significant difference in the postprandial glucose levels at the end of pregnancy ($P < 0,001$). There were no significant differences between groups in fasting glucose level at the end of pregnancy, rate of complications in pregnancy and during labour and delivery, body weight, body fat percentage and weight gain during specific time points of pregnancy, neonatal Apgar scores, neonatal body mass and ponderal index. There was a significant difference in neonatal body mass index which was a little higher in experimental group ($P = 0,035$). Our results clearly confirm positive effect of exercise on postprandial

glucose levels at the end of pregnancy. Also, exercise proved to be perfectly safe as an adjunctive therapy for GDM. Therapeutic exercise during pregnancy might be an effective and safe method for treatment of GDM, along with other lifestyle measures.

Priloga 1

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# IZJAVA O AVTORSTVU

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pod mentorstvom prof. dr. Rado Pišot in somentorstvom prof. dr. Marina Ivanišević

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# LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| ACSM | American College of Sports Medicine |
| ACOG | American College of Obstetricians and Gynecologists |
| ADA | American Diabetes Association |
| AE | Aerobic exercise |
| BF% | Body fat percentage |
| BMI | Body mass index |
| bpm | Beats per minute |
| CG | Control group |
| *d* | Cohen's d |
| diff. | Difference |
| EG | Experimental group |
| FHR | Fetal heart rate |
| FPG | Fasting plasma glucose |
| GDM | Gestational diabetes mellitus |
| GI | Glycaemic index |
| GLUT 4 | Glucose transporter type 4 |
| HAPO | Hyperglycaemia and Pregnancy Adverse Outcome |
| HbA1c | Glycated haemoglobin |
| HDL | High-density lipoprotein |
| HIT | High-intensity training |
| HOMA-IR | Homeostasis Model Assessment of Insulin Resistance |
| HPL | Human placental lactogen |
| HR | Heart rate |
| HRmax | Maximal heart rate |
| IADPSG | International Association of Diabetes and Pregnancy Study Groups |
| IOM | Institute of Medicine |
| ISO | International Standards Organization |
| LDL | Low-density lipoprotein |
| LGA | Large for gestational age |
| Max | Maximum |
| MET | Metabolic equivalent |
| Min | Minimum |
| MNT | Medical nutrition therapy |

| | |
|---|---|
| N | Sample size |
| NELIP | Nutrition and Exercise Lifestyle Intervention Program |
| NICE | National Institute for Health and Clinical Excellence |
| NPH | Neutral protamine hagedorn |
| OGTT | Oral glucose tolerance test |
| PA | Physical activity |
| PI | Ponderal index |
| PPAQ | Pregnancy Physical Activity Questionnaire |
| *r* | Pearson's correlation coefficent |
| $r_{pbi}$ | Point-biserial correlation coefficient |
| RE | Resistance exercise |
| RHI | Regular human insulin |
| RT | Resistance training |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RPE | Rating of perceived exertion |
| SD | Standard deviation |
| SFTM | Skinfold thickness measures |
| $VO_2$max | Maximal oxygen uptake |
| TA30 | Total activity in 30th week of pregnancy |
| TA36 | Total activity in 36th week of pregnancy |
| TALI30 | Total activity of light intensity and above in 30th week of pregnancy |
| TALI36 | Total activity of light intensity and above in 36th week of pregnancy |
| T1DM | Type I diabetes mellitus |
| T2DM | Type II diabetes mellitus |
| THR | Target heart rate |
| TNFα | Tumour necrosis factor alpha |
| WHO | World Health Organization |

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# 1 INTRODUCTION

Pregnancy is a unique state associated with considerable physiological and psychological changes which could promote sedentary behaviours and/or low physical activity levels in women (Symons Downs, Chasan-Taber, Evenson, Leiferman & Yeo, 2012). Exercise is associated with significant beneficial physiological and metabolic changes and response to physical exertion does not differ significantly compared to the nonpregnant condition (Ferraro, Gaudet & Adamo, 2012). Due to a significant increase in obesity and sedentary lifestyle related diseases, physical activity became the core theme in health promotion and disease prevention.

Physical activity includes any bodily movement which substantially increases energy expenditure, whereas exercise is the subset of planned, structured, and repetitive movements done to develop or maintain physical fitness, which includes cardiovascular, strength, and flexibility training options (Haskell et al., 2007; Nelson et al., 2007). Aerobic exercise involves repetitive movements that increase heart rate for an extended duration of time with a concomitant increase in core body temperature (McDermott & Mernitz, 2006). Resistance training exercises use muscles to generate a force to move or resist weight (Beachle & Earle, 1995; McDermott & Mernitz, 2006).

Effects of physical activity and exercise on health are well known, but some aspects still need more research. Physically active population has lower rates of coronary heart disease, hypertension, cerebrovascular insult, type 2 diabetes mellitus, metabolic syndrome, colon and breast cancer, and depressive disorders (Physical Activity Guidelines Advisory Committee, 2008). Physical activity also has a positive effect on the functional abilities of muscle and cardiorespiratory system, body weight and composition, as well as bone density.

Formerly, pregnant women were advised to limit their physical activity levels due to the fear of spontaneous abortion and preterm birth (American College of Obstetricians and Gynecologists, 1985). Recently, however, physical activity in pregnancy has started to be studied in a more traditional chronic disease prevention approach, with specific research areas including the role of physical activity on pregnancy induced hypertension, gestational diabetes, musculoskeletal

disorders, breastfeeding and weight loss, mental health, and offspring health and development (American College of Sports Medicine, 2006). Today, physical activity is a part of antenatal care with the most recent guidelines (ACOG, 2002; Davies, Wolfe, Mottola, MacKinnon & Society of Obstetricians and Gynecologists of Canada, SOCG Clinical Practice Obstetrics Committee, 2003) being proactive and suggesting that all pregnant women without contraindications can benefit from physical activity during pregnancy.

## 1.1 Metabolic adaptations in pregnancy

Pregnancy is accompanied by a series of anatomical, physiological and biochemical adaptations all of which begin soon after conception and continue throughout the pregnancy (Hytten, 1991). Most changes are caused by the maternal response to the physiological stimuli of the fetus and the placenta and occur in nearly every organ system due to the increased demands of the growing fetus and placenta.

Pregnancy is a dynamic, anabolic state with the first half acting as a preparation period for the demands of rapid fetal growth in the second half of the pregnancy. Within a few weeks after conception, the placenta, a new endocrine organ, starts to develop and secrete hormones and cytokines which affect the metabolism of all nutrients. These adaptations support fetal growth and development, but they also support homeostasis in the mother and prepare her for lactation. One or more adaptations take place: 1. growth of new tissue or deposition of nutrients in maternal reserves, 2. redistribution between tissues, and 3. increased turnover or metabolism of substances (King, 2000).

Changes in glucose metabolism, as well as fatty acids, occur simultaneously with mother's and fetus' increased energy demands, whereas the adaptation of protein metabolism appears to occur in anticipation of maternal and fetal demands (Kalhan, 2000). The primary energy source for the fetus is glucose, and nitrogen accretion and protein deposition are essential for the synthesis of new fetal and maternal tissues. Changes in nutrient metabolism can be described by the following general statements: 1. they are caused by hormonal changes, fetal demands and maternal nutrient supply, 2. there is more than one potential adaptation for each nutrient, 3. changes in mother's behaviour affect physiological adaptations and 4. physiological

capacity of nutrient metabolism adaptation has a limit which, if exceeded, causes impaired fetal growth and development (King, 2000).

Pregnancy-induced adaptations in maternal physiology primarily protect the fetus by ensuring that metabolic demands of both the mother and the fetus are met (Ferraro et al., 2012). The fetus is not deprived of substrate during maternal exercise if the mother's nutrition is adequate (Bessinger & McMurray, 2003; Gavard & Artal, 2008). Exercise throughout pregnancy increases the parenchymal component of the placenta, total vascular volume, site-specific capillary volume and surface area, and other parameters associated with an enhanced rate of placental perfusion and transfer function (Jackson, Gott, Lye, Ritchie & Clapp, 1995).

### 1.1.1 Basal metabolism and weight gain

The average weight gain in pregnancy is approximately 12.5 kg (Hytten, 1991). Forty percent of the total weight gain is comprised of the weight of the fetus, placenta and amniotic fluid and the remaining 60% represents an increased mass of maternal tissue including the uterus, breasts, blood, adipose tissue and extracellular fluid (Pitkin, 1977). Standards on weight gain in pregnancy were proposed in 1990 and further modified in 2009 and 2013 (Institute of Medicine, 1990; IOM 2009; IOM 2013). These guidelines set different recommendations for undernourished, well-nourished, and overweight and obese pregnant women.

There is one or more adaptations for the preservation of energy: 1. decreasing lipid synthesis and the deposition of maternal adipose tissue, 2. change in the intensity of physical activity and 3. increase in food and energy intake (King, 2000). By the third trimester, maternal basal metabolic rate increases by 10-20%, with an additional 10% increase in twin pregnancies (Shinigawa, Suziki, Chihara, Otsubo, Takeshita & Araki, 2005). Basal metabolic rates are 20% higher in pregnant obese pregnant women in comparison with the period before pregnancy (Bronstein, Mak & King, 1995).

Increase in adipose tissue deposits correlates positively with gestational weight gain. Deposition of fat occurs during the second half of pregnancy and is assumed to represent the energy deposits to be used in the final quarter of the pregnancy to fulfill increased fetal energy demands. The total gain of adipose tissue is 3.35 kg

on average, ranging from -2 to 10kg in healthy women (King, Butte, Bronstein, Kopp & Lindquist, 1994), i.e. 1.9 to 5.8 kg (Nelson, Matthews & Poston, 2010). Total energy requirements of an average pregnancy from the beginning until the end approximately equal 80000 kcal, with 300 additional kcal per day respectively (Hytten, 1991). Excessive fat deposits can have harmful effects on both the pregnant women and her fetus. Maternal obesity increases the risk of numerous complications during pregnancy (Nelson et al., 2010) since fat mainly deposits centrally in the subcutaneous truncal and visceral adipose tissue. Central adipose tissue is related to cardiovascular diseases and diabetes mellitus in adults, and glucose intolerance/gestational diabetes and gestational hypertension/preeclampsia in pregnant women. Obese pregnant women have elevated levels of inflammatory mediators which contribute to risk increase.

Benefits of physical activity in pregnancy, among others, include limiting excess maternal weight gain and attenuation of pregnancy-induced insulin resistance (Wolfe, Heenan & Bonen, 2003). Also, benefits on body mass, fat mass and cardiovascular profile last for several years postpartum (Clapp, 2008). The effects of physical activity in pregnancy will be discussed in detail in subsequent chapters.

### 1.1.2 Metabolism of carbohydrates

Normal pregnancy is characterised by mild fasting hypoglycaemia, postprandial hyperglycaemia and hyperinsulinaemia (Hytten, 1991). Pregnant women, after oral ingestion of glucose, have prolonged hyperglycaemia and hyperinsulinaemia, as well as increased supression of secretion of glucagon (Phelps, Metzger & Freinkel, 1981). This is the consequence of an induced state of peripheral insulin resistance which has the purpose to maintain postprandial supply of glucose to the fetus. Estimation of fetal utilization of glucose in late pregnancy is 20-25g per day (Butte, 2000).

In early pregnancy, basal glucose and insulin concentration do not differ significantly from pre-pregnancy condition. Until the third trimester, basal concentration of glucose is 0.56-0.83 mmol/L lower and concentration of insulin is almost double than in non-pregnant condition (Butte, 2000). Postprandial glucose concentration is elevated, with peak glucose levels retained for a longer period

(Butte, 2000). Basal endogenous hepatic glucose production is increased by 16-30% (Butte, 2000).

Levels of fasting glucose progressively decrease with the advancement of pregnancy, and in cases of prolonged fasting they decrease even further. Potential contributing factors include: 1. effects of dilution (elevated plasma volume in early pregnancy), 2. elevated glucose consumption (or increased fetoplacental glucose consumption, or increased maternal glucose deposition, due to elevated β-cell function) and/or 3. insufficient glucose production (limited hepatic production in relation to circulating glucose concentrations) (Lain & Catalano, 2007).

Despite decreased fasting glucose levels and elevated fasting insulin levels, hepatic glucose production is increased. This contributes to decreased insulin sensitivity and leads to decreased suppression of hepatic glucose production in women with normal glucose tolerance. Obese pregnant women with abnormal glucose tolerance have an impaired ability to completely suppress hepatic glucose production in late pregnancy when compared to pre-pregnancy and early pregnancy condition. This indicates further decrease in insulin sensitivity.

Insulin sensitivity during pregnancy is characterised as a postreceptor deficit which results in decreased insulin ability to stimulate glucose transporter type 4 (GLUT4) mobilisation from the interior to the surface of the cell (Catalano, 2010). Human placental lactogen (HPL) has mainly been mentioned as the cause of decreased insulin sensitivity (Ryan & Enns, 1988), but there is also the influence of cytokines and elevated levels of lipids during pregnancy, which correlate positively with longitudinal changes in insulin sensitivity, in both non-pregnant (Hotamisligil, Murray, Choy & Spiegelman, 1994) and pregnant populations (Xiang, Peters, Trigo, Kjos, Lee & Buchan, 1999; Kirwan et al., 2002). Insulin sensitivity in early pregnancy varies and depends on maternal pre-pregnancy sensitivity. Pregnant women with a small amount of adipose tissue have a 10% decrease in insulin sensitivity on average, and obese pregnant women have a 15% increase in insulin sensitivity in early pregnancy (Catalano, Huston, Amini & Kalhan, 1999). A decreased need for insulin in early pregnancy is especially prominent in obese women with decreased insulin sensitivity prior to conception. In late pregnancy, peripheral insulin sensitivity further decreases, with the decrease ranging from -33% to -78% (Lain & Catalano, 2007), where pregnant women with less adipose tissue have lower overall decrease in insulin sensitivity.

A normal response to insulin resistance is an increase in insulin secretion. Increased insulin secretion during pregnancy is most likely a compensatory mechanism for progressive insulin resistance. Insulin secretion increases by 50% early in the second trimester (Reece, Coustan & Gabbe, 2004), before the manifestation of insulin resistance, which means that hormonal characteristics may be responsible for increased insulin secretion, regardless of insulin resistance. Mechanisms responsible for the decrease of insulin sensitivity are not entirely known. Partially, they are related to several hormones, like HPL, progesterone, prolactin, cortisol, and cytokines, which are all elevated in pregnancy (Lain & Catalano, 2007). Circulating levels of tumour necrosis factor alpha (TNFα) are inversely correlated with insulin sensitivity and TNFα is a good predictor of insulin sensitivity from pre-pregnancy to late pregnancy (Lain & Catalano, 2007). An elevated concentration of circulating free fatty acids also increases resistance to insulin (Freemark, 2006).

There is an increased carbohydrate contribution to the oxidative metabolism in late pregnancy. The twenty-four hour respiratory quotient, measured by respiratory calorimetry, is significantly higher in late pregnancy than in postpartal period; carbohydrate oxidation expressed as a percentage of the consumption of non-protein energy sources decreases from 66% in late pregnancy to 58% six months postpartum, and absolute carbohydrate oxidation values are significantly higher during pregnancy (292 g per day) than postpartum (210 g per day) (Butte, 2000).

### 1.1.3 Metabolism of lipids

Although the changes in glucose metabolism are often regarded as the primary metabolic adaptation during pregnancy, there are also significant changes in the metabolism of lipids. One of the most prominent and consistent changes in lipid metabolism during pregnancy is hyperlipidaemia.

Non-obese women deposit approximately 3.5 kg of fat during normal pregnancy, with some individual variations (King et al., 1994). Adipose tissue is deposited primarily in mid-pregnancy, with more deposits located centrally than peripherally (Hytten & Thomson, 1968; Pipe, Smith, Halliday, Edmonds, Willians & Coltart, 1979). The ratio of preperitoneal and subcutaneous adipose tissue changes and there is an increase in intra-abdominal adipose tissue which can be related to decreased insulin sensitivity (Lain & Catalano, 2007).

Lipid, lipoprotein and apolipoprotein values in the plasma significantly increase during pregnancy. Total triglyceride levels increase 2-4 times, total cholesterol by 25-50%, low-density lipoproteins (LDL) by 50%, and high-density lipoproteins (HDL) by 30% by mid pregnanacy, followed by a slight decline at the end of pregnancy (Lain & Catalano, 2007).

Hyperlipidaemia is the most prominent in pregnant women with gestational diabetes mellitus (GDM) (Catalano, Nizielski, Shao, Preston, Qiao & Friedman, 2002). The mechanisms responsible for this include increased lipolytic activity and decreased activity of lipoprotein lipase in adipose tissue (Herrera, Amusquivar, Lopez-Soldado & Ortega, 2006). The effects of estradiol and progesteron on the liver also have an important role (Desoye, Schweditsch, Pfeiffer, Zechner & Kostner, 1987). After delivery, concentrations of lipids, lipoproteins and apolipoproteins decrease, which is even more accelerated by lactation (Darmady & Postle, 1982).

Decreased insulin ability to supress lipolysis in late pregnancy is related to increased concentrations of free fatty acids. Elevated free fatty acids are a useful energy source for maternal needs in late pregnancy, and they are also related to higher birth weight of the infant (Catalano, 2010). There is a significant positive correlation between maternal triglyceride concentrations in late pregnancy, and fetal growth/adiposity (Di Cianni et al., 2005; Schaefer-Graf, 2008). The shift from the anabolic to the catabolic state stimulates the use of lipids as maternal energy source, preserving glucose and amino acids for the fetus at the same time.

Changes in lipid metabolism stimulate the accumulation of maternal fat deposits in early and mid pregnancy. In late pregnancy, they also improve adipose tissue mobilisation available for transfer to the placenta during the last trimester, when fetal growth is the most prominent and there are high demands for essential fatty acids (Herrera et al., 2006; Innis, 2005). In lean women, lipogenesis is predominant in the first stage of pregnancy, and lipolysis in the late stage, while in obese women lipolysis predominates in both stages of pregnancy (Lain & Catalano, 2007). This offers further evidence of increased insulin resistance in obese women.

Adipose tissue is not only a source of energy, but also an active metabolic tissue. Adipocytes and adipose stromal cells are a rich source of cytokines and inflammatory mediators. These can both increase insulin resistance (TNFα), and

reduce it (adiponectin). Their influences on metabolic changes in pregnancy are not entirely known. The interaction between cytokines in maternal adipose and placental tissue could play a much more important role in the regulation of metabolism of pregnant women than it was previously believed.

### 1.1.4 Metabolism of proteins

Significant adaptations also take place in protein metabolism in pregnancy. They are complex, change gradually during pregnancy and their purpose is to satisfy the increasing demands of the fetus. While adaptations of glucose and fatty acids metabolism start happening when the demands for energy are increased, changes in protein metabolism are anticipatory of these demands. There is a decrease in overall α-amino nitrogen, a decrease in urea synthesis and in the rates of transamination of branched-chain amino acids (Kalhan, 2000). The metabolism of proteins in pregnancy is directed towards the deposition of nitrogen and protein. Initially, this deposition is directed to the pregnant woman's body, and later to the fetal body as well. The exact mechanism of this adaptation is not entirely known, but it is probably related to pregnancy-induced insulin resistance (Kalhan, 2000).

In the final stage of pregnancy, the fetus and placenta reach the mass of approximately 4 kg and contain ca. 500 g of protein, which is around half of the total protein deposit in pregnancy, estimated at 925 g (Duggleby & Jackson, 2002). The remaining amount of these proteins is deposited in the uterus, in the form of contractile proteins, in mammary glands and in the blood (Cunningham, Leveno, Bloom, Hauth, Rouse & Spong, 2010).

Increase of amino acids concentration in the fetus is regulated by the placenta. The placenta is not only responsible for the concentration of amino acids in fetal circulation, but also for the synthesis of proteins, oxidation and transamination of certain amino acids (Galan, Marconi, Paolini, Cheung & Battaglia, 2009). The concentration of amino acids is higher in the fetus than in the mother (Cetin et al., 2005; van den Akker et al., 2009).

Most amino acids during pregnancy are used for protein synthesis, with a decrease in their oxidation by approximately 10% (Duggleby & Jackson, 2002). Although there is no increase in measured protein synthesis in the first trimester, there is a

15% increase in the second, and 25% increase in the third trimester (Duggleby & Jackson, 2002). These changes are disproportionate to the highly active protein synthesis in the fetus and the placenta. This indicates a general increase in protein synthesis in maternal tissues. Nitrogen retention in a pregnant woman's organism is greater than the estimated protein uptake in pregnancy (King, 1975) and it reaches its full potential during the final quarter of pregnancy. On the other hand, adaptations of maternal nitrogen metabolism occur early in gestation, before significant increases in nitrogen supply to the fetus. As calculated by Calloway (1974) nitrogen retention between the 20th and the 40th week of pregnancy is approximately 1.3 g per day. Measuring nitrogen balance proved a more efficient utilisation of proteins from food in pregnancy. Nitrogen retention levels are, on average, 0.2 g per day before pregnancy, -0.4 g per day in the 12th week of pregnancy, 0.5 g per day in the 23rd week and 1.2 g per day in the 34th week (Mojtahedi, de Groot, Boekhold & van Raaij, 2002), so lower than previously calculated by Calloway.

### 1.1.5 Metabolism of water, electrolytes and minerals

Increased water retention is a normal physiological manifestation during pregnancy which starts in the early stages of pregnancy. It is partially caused by decreased plasma osmolality of approximately 10 mOsm/kg, induced by changes in osmotic threshold for thirst and vasopressin secretion (Lindheimer & Davison, 1995; Heenan, Wolfe, Davies & McGrath, 2003). The amount of water in fetus, placenta and amniotic fluid is approximately 3.5 L until term, with additional 3 L of water accumulated due to increased blood volume, uterus and breasts. This makes the minimal amount of additionally accumulated fluid in normal pregnancy approximately 6.5 L (Hytten, 1991).

During normal pregnancy a woman retains approximately 1000 mEq of sodium and 300 mEq of potassium (Lindheimer, Richardson, Ehrlich & Katz, 1987). Despite elevated glomerular filtration of sodium and potassium, excretion of these electrolytes is not changed during pregnancy due to tubular reabsorption (Pitkin, 1977; Brown, Sinosich, Saunders & Gallery, 1986). Despite the increase in their overall accumulation, their serum concentrations are mildly reduced, due to expanded plasma volume. Serum concentrations remain very close to the normal

values of non-pregnant women (Kametas, McAuliffe, Krampl, Sherwood & Nicolaides, 2003).

There are also substantial changes in calcium and bone metabolism, as well as changes in bone-mineral status during pregnancy. The overall level of serum calcium concentration decreases during pregnancy, reflecting decreased plasma albumin concentration, as well as the consequential decrease in calcium-binding proteins. Levels of serum ionized calcium remains the same (Power et al., 1999). A developing fetus has a considerable effect on maternal calcium homeostasis because, by term, fetal skeleton accumulates approximately 30 g of calcium, 80% of which is accumulated during the third trimester (Sowers, 1996). Most of the accumulated calcium is used from maternal calcium deposits, but the pregnant women satisfy the increased fetal calcium demands by doubling intestinal calcium absorption, partly mediated by 1.25-dihydroxy vitamin D3 (Kovacs & Fuleihan, 2006). Hyperoestrogenaemia and weight gain in pregnancy both have protective effects on bones.

Magnesium levels in serum also decline during pregnancy. When compared to non-pregnant women, pregnant women have considerably lower levels of total and ionised magnesium (Kametas et al., 2003). Serum phosphate levels are the same as in non-pregnant women, but the renal threshold for inorganic phosphate excretion is increased during pregnancy, due to elevated calcitonin levels (Weiss, Eisenstein, Ramot, Lipitz, Shulman & Frenkel, 1998). Metabolism of other minerals and elements is not significantly affected, except their retention necessary for the growth of the fetus and the increased need for iron.

### 1.1.6 Metabolic dysregulation in pregnancy

Due to metabolic changes during pregnancy, especially decreased insulin sensitivity, overweight and sedentary pregnant women face a higher risk of metabolic dysregulation during pregnancy, especially gestational diabetes mellitus, preeclampsia and fetal macrosomia (Sklempe Kokic, 2013). Pregnancy is a state of metabolic stress and potential risk factor for metabolic syndrome, diabetes and cardiovascular disease in the future. Women affected by metabolic disorders during pregnancy face an increased risk of metabolic syndrome later in life, especially if they gain weight in the postpartal period (Villamor & Cnattingius, 2006). The risk of

premature cardiovascular diseases is closely related to the severity of metabolic disorders during pregnancy (Ray, Vermuelen, Schull & Redelmeier, 2005).

Hypertensive disorders in pregnancy double the risk of developing hypertension and cardiovascular diseases later in life (Mass, van't Hof & de Boer, 2007). Pathophysiology of GDM results in a cumulative incidence of T2DM from 2.6% to over 70% in studies that examined women from 6 weeks postpartum to 28 years postpartum (Kim, Newton & Knopp, 2002).

The assumption is that normal pregnancy in itself stimulates an inflammatory response, which is excessive in preeclampsia, and triggers endothelial dysfunction in uterine circulation, probably makes the placenta the ultimate source of inflammatory stimulus (Redman, Sacks & Sargent, 1999). Intrauterine environment and metabolic disorders also influence developmental processes of the fetus and have long-lasting effects on their health (El Hajj, Schneider, Lehnen & Haaf, 2014).

## 1.2 Exercise in pregnancy

In the past twenty years there has been a great increase in research on the impact of physical exercise on the wellbeing of pregnant women and their fetuses. Many women of childbearing age choose to continue their exercise practice during pregnancy. Pregnancy is often the time when women take steps to change their unhealthy lifestyle habits and many previously sedentary women chose to start exercising during pregnancy. This emphasizes the need to clarify the effects of different types of exercise on the health of both mother and fetus, short-term as well as long-term.

Few studies have been conducted in different countries regarding the levels of physical activity of pregnant women. Only 15.8% of women are engaged in exercise during pregnancy at the recommended level (Evenson, Savitz & Huston, 2004). From the cohort of healthy women in Ireland, who had no contraindications for exercise during pregnancy, only 21.5% met the current recommendations for exercise in pregnancy (Walsh, McGowan, Byrne & McAuliffe, 2011). Danish nulliparous women decreased the intensity and the time spent on exercise and increased sedentary activity during pregnancy in comparison to pre-pregnancy

condition (Hegaard et al., 2011). The prevalence of British pregnant women engaged in physical activity sufficient to cause sweating for 3h/week or more, was 48.8% at 18 weeks of pregnancy and similar at 32 weeks. About two out of three of these women reported reducing physical activity levels at 18 weeks of gestation (Liu, Blair, Teng, Ness, Lawlor & Riddoch, 2011). Only 4.3% pregnant women in Brazil were active during the entire pregnancy and 12.9% of them reported engaging in some type of physical activity during pregnancy (Domingues & Barros, 2007).

In general, the prevalence of active pregnant women, as well as duration, frequency and intensity of exercise, are lower in comparison with non pregnant adult female population and do not meet current recommendations (Evenson et al., 2004; Domingues & Barros, 2007).

Globally, 31.1% of adults are physically inactive, and women are more inactive (33.9%) than men (27.9%) (Hallal et al., 2012). Specifically, 43.3% of people are inactive in Americas, 43.2% in the eastern Mediterranean and 34.8% in Europe (Hallal et al., 2012). In England, 55% of women met physical activity guidelines in 2012 (Joint Health Surves Unit, 2013) and only 21.1% Spanish women met recommended levels of leisure time physical activity (Meseguer, Galán, Herruzo, Zorrilla & Rodríguez-Artalejo, 2009). In Croatia, 31.9% of women are physically inactive (Milošević, Golubić, Mustajbegović, Doko Jelinić, Janev Holcer & Kern, 2009). At least 25.1% female university students do not meet physical activity recommendations of World Health Organization (WHO) and 37.9% of female university students do not meet the physical activity levels recommended for additional health benefits by the WHO (Pedišić, Rakovac, Bennie, Jurakić & Bauman, 2014).

Cochrane review of the effects of aerobic exercise on healthy pregnant women concluded that the available data are insufficient to infer important risks or benefits for the mother or infant (Kramer & McDonald, 2006). However, the authors concluded that regular exercise during pregnancy appears to improve (or maintain) physical fitness (Kramer & McDonald, 2006).

A large number of clinical trials have been conducted to assess the effects of exercise on different outcomes for pregnant women and their fetuses, from musculoskeletal disorders, depression, quality of life, gestational weight gain,

gestational diabetes and insulin resistance, cardiovascular fitness, to growth and development of the fetus.

Musculoskeletal disorders, especially lower back pain and pelvic girdle pain are very common among pregnant women (Pennick & Liddle, 2013). Recent Cochrane review shows moderate-quality evidence that exercise significantly reduces evening pelvic pain or lumbo-pelvic pain in comparison with the usual care, and low-quality evidence that exercise significantly reduces pain and disability from low back pain (Pennick & Liddle, 2013). A large Norwegian study (Stafne, Salvesen, Romundstad, Stuge & Mørkved, 2012a) found no significant difference in the prevalence of lower back pain at 36 weeks of healthy pregnant women who exercised for 12 weeks during their pregnancy. Another trial conducted on South African population showed that a 10-week exercise program decreased back pain intensity and increased functional ability during pregnancy (Kluge, Hall, Louw, Theron & Grové, 2011).

Exercise in pregnancy is also beneficial for the prevention of excessive weight gain (Hui et al., 2012; Nascimento, Surita, Parpinelli, Siani & Pinto e Silva, 2011; Haakstad & Bø, 2011a; Phelan, Phipps, Abrams, Darroch, Schaffner & Wing, 2011). Also, physical exercise could have an important role in the prevention of preeclampsia (Dempsey, Butler & Williams, 2005; Kasawara, Nascimento, Costa, Surita & Pinto e Silva, 2012).

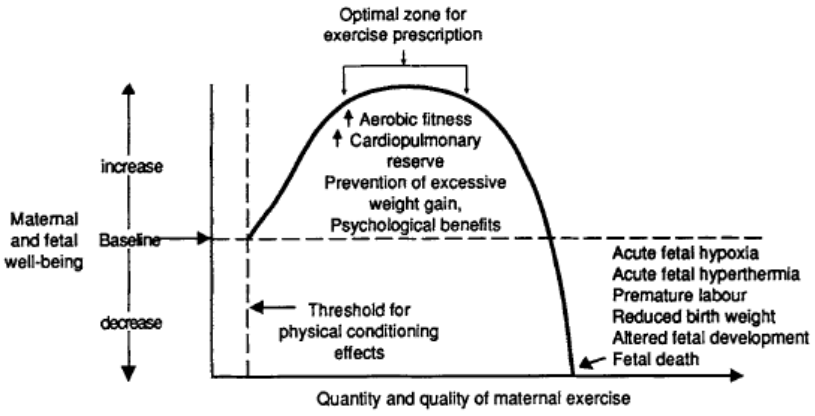
There are also positive effects on depression during pregnancy and postpartum (Robledo-Colonia, Sandoval-Restrepo, Mosquera-Valderrama, Escobar-Hurtado & Ramírez-Vélez, 2012; Songøygard, Stafne, Evensen, Salvesen, Vik & Mørkved, 2012). Quality of life is also positively affected by exercise (Nascimento et al., 2011; Vallim, Osis, Cecatti, Baciuk, Silveira & Cavalcante, 2011), as well as maternal perception of health status (Barakat, Pelaez, Montejo, Luaces & Zakynthinaki, 2011).

Exercise does not harm the fetus (Nascimento et al., 2011; Barakat et al., 2011; Haakstad & Bø, 2011b). On the contrary, maternal physical activity could be beneficial for the fetus, since a recent review showed that children born to obese mothers or those who gained excessive weight have an increased risk of obesity, T2DM and metabolic syndrome themselves (Adamo, Ferraro & Brett, 2012). Physical activity in pregnancy does not increase the risk of delivering a small for gestational age newborn (Hegaard, Pedersen, Nielsen & Damm, 2007), however, it

reduces the odds of delivering a large for gestational age (LGA) newborn (Alderman, Zhao, Holt, Watts & Beresford, 1998; Juhl, Olsen, Andersen, Nohr, Andersen, 2010). Furthermore, physical activity in pregnancy has a protective effect on preterm delivery risk (Mudd, Owe, Mottola & Pivarnik, 2013). Also, children of exercising women are lighter and leaner at birth and continue to be significantly leaner at the age of 5 compared to children of non-exercising women (Clapp, 1996). On top of this, there is inverse relationship between physical activity in the third trimester with toddler weight and weight-for-height *z*-score at 18-24 months of age (Mattran, Mudd, Rudey & Kelly, 2011). Limited evidence suggests that maternal physical activity does not impact the mode of delivery (Ferraro et al., 2012).

Existing data suggest that there is a dose-response curve for exercise in pregnancy and it appears that exercising in the optimal zone for exercise quality and quantity can result in significant benefits for pregnant women (Wolfe, Hall, Webb, Goodman, Monga & McGrath, 1989a) (Figure 1). On the other hand, overexertion could endanger the fetus and its development (Wolfe et al., 1989a). The interaction between exercise intensity and duration should be taken into account when planning exercise sessions for pregnant women because there is the need to allow proper metabolic heat dissipation, adequacy of uterine blood flow, fetal oxygen delivery and fetal carbohydrate availability (Wolfe et al., 1989a). Exercise should be balanced to avoid harmful effects to the fetus and achieve physiological benefits for both the mother and fetus.

*Figure 1: Hypothetical dose-response curve for aerobic-type conditioning during pregnancy.*




*Source: Wolfe, Ohtake, Mottola & McGrath, 1989b; Lotgering, Gilbert & Longo, 1984; Lotgering & Longo, 1984; Lotgering, Gilbert & Longo, 1985.*

Finally, exercise in pregnancy has an important role in the prevention of GDM and could have an important role in the treatment of GDM which will be further discussed in detail in the following chapters.

Numerous studies proved beneficial effects of exercise in pregnancy, which supports current guidelines for exercise during healthy pregnancy. Also, a number of studies confirmed inadequate levels of physical activity among pregnant women in different countries, which needs improvement. There is still not enough evidence regarding the effects of exercise in pathological conditions during pregnancy, such as hypertension and GDM.

## 1.3 Exercise recommendations for pregnant women

Current recommendations of the American College of Obstetricians and Gynecologists (ACOG) (2002) are in accordance with the American College of Sports Medicine (ACSM) – Centers for Disease Control and Prevention's general guidelines for physical activity which recommend 30 min or more of moderate physical activity per day in the majority of, or preferably all days of the week (Nelson et al., 2007). For women who were active before pregnancy, the recommendation is that they may continue with their activities, but change intensity and frequency over the course of pregnancy (ACOG, 2002; Nelson et al., 2007). There are also other published guidelines for exercise in pregnancy, like the Canadian guidelines for exercise during pregnancy (Davies et al., 2003) and recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG, 2006) with similar content.

Aerobic exercise, which involves large muscle groups, is recommended to maintain cardiovascular fitness, prevent chronic diseases and excessive weight gain. Recommended activities include walking or jogging, using stationary bicycle, treadmill, swimming, water aerobics, dance, and low-impact aerobics (ACOG, 2002; Davies et al., 2003; RCOG, 2006). Activities which include potential trauma or the risk of falling should not be performed (ACOG, 2002; Davies et al., 2003; RCOG, 2006). Also, supine position during the second half of pregnancy should be avoided in order to prevent compression of the inferior vena cava. Valsalva maneuver should also be avoided.

Recently, Zavorski & Longo (2011) recommended adding strength training to the routine exercise for pregnant women. They suggest that light strength training during the second and third trimester does not affect newborn size or overall health. Authors recommend performing light strength training once or twice per week on nonconsecutive days, with 8 to 10 strength exercises per session. Adding this type of training could possibly lead to benefits of increasing overall body strength, good posture and body core strengthening, and contribute to easier labour and birth, as well as prevent musculoskeletal discomforts and metabolic disorders (Pennick & Liddle, 2013). However, caution is recommended with resistance exercise in order to prevent overexertion, overstretch and minimise the risk of injury to connective and muscle tissues (Nascimento, Surita & Cecatti, 2012). Also, it is recommended to add pelvic floor muscle exercises to the exercise routine (Boyle, Hay-Smith, Cody & Mørkved, 2008).

Exercise intensity can be assessed in different ways. It can be measured as the variation in the heart rate (HR) increase with exertion compared to the HR at rest or to the maximum HR (or peak rate) (Nascimento et al., 2012). Proposed target zones for aerobic exercise according to each age decade are: <20=140-155; 20-29=135-150; 30-39=130-145; ≥40=125-140 beats/min, which corresponds to around 60-80% of aerobic capacity (Artal & O'Toole, 2003). For overweight and obese pregnant women, target zones are more conservative according to each age decade: 20-29=110-131; 30-39=108-127 beats/min (Ferraro et al., 2012). Ratings of perceived exertion can also be used to measure the intensity of exercise (Borg, 1982). Borg scale rates from 6 to 20, and target zone for pregnant women is recommended to be 12-14 which represents "somewhat hard" perception of exercise (Artal & O'Toole, 2003). The third method for the assessment of the intensity of exercise is the "talk test" which responds to exercising at the level of intensity that allows pregnant women to carry on a conversation. If a pregnant women is able to keep up a conversation, this confirms that the intesity of exercise is adequate and there is no overexertion (RCOG, 2006).

Regarding the duration of exercise there are two main concerns: thermoregulation and energy balance. Exercise, especially prolonged (longer than 45 min), should be performed in a thermoneutral environment or in controlled environmental conditions. Pregnant women should be properly hydrated and overexertion should be avoided. Energy costs should be estimated and balanced by appropriate energy intakes (Artal & O'Toole, 2003). Setting limits on exercise duration is not possible

because of the reciprocal relation between exercise intensity and duration (Artal & O'Toole, 2003). ACOG (2002) recommends to accumulate 30 minutes or more of moderate physical activity per day, but does not specify the maximum duration of a continuous exercise session. Pregnant women who have been sedentary before pregnancy should gradually progress with their exercise, and pregnancy should not be the period for great improvements in physical fitness. Women who were active before pregnancy may keep their levels of exercise or perform at least moderate-to-vigorous exercise four times a week in sessions of 30 min or more (Artal & O'Toole, 2003).

Exercise recommendations for pregnant women are not much different from guidelines for non-pregnant adult population. Physical Activity Guidelines Advisory Committee (2008) recommends 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity every week, and muscle strengthening activities on 2 or more days a week for all major muscle groups for non-pregnant adult population. American College of Sports Medicine also recommends at least 150 minutes of moderate-intensity exercise each week for most adults (Garber et al., 2011). These guidelines recommend 30-60 minutes of moderate-intensity exercise five days a week or 20-60 minutes of vigorious-intensity exercise three days a week. Resistance exercises are also recommended two or three days per week for all major muscle groups. These recommendations are also in consensus with those published by WHO (2010) and UK Department of Health (2011).

# 2 GESTATIONAL DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterised by a deficit in insulin secretion by pancreatic β-cells, insulin action or both, and the most common types of diabetes mellitus are type 1 and type 2. Gestational diabetes mellitus is defined as any carbohydrate intolerance first diagnosed during pregnancy (Metzger et al., 2007). It accounts for 90-95% of all cases of diabetes in pregnancy and it is the most common metabolic disorder in pregnancy (American Diabetes Association (ADA), 2015; Landon & Gabbe, 2011). The prevalence of GDM is up to 14% (ADA, 2015; ACOG, 2013) and it is directly related to the prevalence of T2DM in a given population (Landon & Gabbe, 2011). The prevalence in Canada is 8-18% (Canadian Diabetes Association, 2008), in China 6.8-10.4% (Hirst, Raynes-Greenow & Jeffery, 2012), in England and Wales 3.5% (National Collaborating Centre for Women's and Children's Health, 2008), and in Italy 10.9% which is 25% greater compared to the one determined using the old criteria 10 years ago (Lacaria et al., 2014). In India, it is exceptionally high with the prevalence of 27.5% (Guariguata, Linnenkamp, Beagley, Whiting & Cho, 2014).

The basic difference between GDM and T2DM is a rapid onset during pregnancy and remission after childbirth. Hyperglycaemia in GDM and T2DM is related to partial inhibition of insulin secretion, as well as increased insulin resistance. Resistance to insulin develops first and, in susceptible individuals, leads to slow, progressive insulin secretion failure (Buchanan, 2001). GDM can, therefore, also be observed as a result of inhibited insulin secretion (Groeller, Lowe, Worsley & Jenkins, 2010), occurring when insulin secretion is insufficient in relation to insulin resistance (Clapp, 2006). Gestational diabetes mellitus shares a common etiology with T2DM (El Hajj et al., 2014). Maternal hyperglycaemia causes excessive transfer of nutrients, especially glucose to the fetus, resulting in fetal hyperinsulinaemia which further causes fetal adiposity, macrosomia and perinatal complications (Jovanovic & Pettitt, 2001; Kjos & Buchanan, 1999).

Risk factors include advanced maternal age, maternal obesity, lack of physical activity and sedentary lifestyle, high parity, previous delivery of macrosomic infant, family history of T2DM, ethnicity (Asian, Caribbean and Middle Eastern descent), maternal short stature, polycystic ovary syndrome, high levels of saturated fat in the diet, low-fibre and high glycaemic index (GI) diet, prior GDM, prior neonatal

death, prior Caesarean delivery, previous stillbirth or congenital malformations, high blood pressure during pregnancy and multiple pregnancy (Xiong, Saunders, Wang & Demianczuk, 2001; Ben-Haroush, Yogev & Hod, 2004). The increase of body mass index by one unit is accompanied by the increase of GDM prevalence by 0.92% (Torloni et al., 2008).

## 2.1 Outcomes and consequences of GDM

GDM is a major cause of perinatal morbidity and mortality, both short-term and long-term (Ashwal & Hod, 2015). It is associated with a variety of adverse outcomes, both for the mother and the fetus. Possible consequences for the mother include increased rate of operative delivery, increased need for labour induction, hypertension during the pregnancy, preeclampsia and future risk for T2DM, metabolic syndrome, obesity, cardiovascular morbidities and reccurent GDM (Estampador & Franks, 2014; Barahona et al., 2005; ADA, 2015). The risk of preeclampsia rises from 5-7% to 15-20% (Yogev, Xenakis & Langer, 2004). This risk is influenced by the severity of GDM and pre-pregnancy body mass index (BMI) (Ehrenberg, Durnwald, Catalano & Mercer, 2004). Both pre-pregnancy obesity and diabetes are independent risk factors for Caesarean delivery (Ehrenberg, Mercer & Catalano, 2004). The risk of future T2DM later in life ranges from 20-80% (Lauenborg et al., 2004; Bian, Gao, Xiong, Xu, Qian & Liu, 2000). There is also an increased possibility of macrosomic or LGA fetus, cephalopelvic disproportion, postpartum hemorrhage, birth trauma and shoulder dystocia (ADA, 2015; ACOG, 2013; Jastrow et al., 2010).

In the long term, women who have suffered from GDM have a 7-8 times higher risk of developing T2DM (Bellamy, Casas, Hingorani & Williams, 2009; Chodick et al., 2010). The cumulative incidence of T2DM in women who have suffered from GDM varies from 2.6 to over 70% after monitoring within a range of 6 weeks and 28 years after birth (Kim et al., 2002). The cumulative proportion of women who develop T2DM 1 year postpartum is 1.7%, 10 years postpartum 17% and 15 years postpartum 25% (Lee, Hiscock, Wein, Walker & Permezel (2007).

The larger the number of pregnancies with GDM, the higher the risk of recurrence in subsequent pregnancies: 35-80%, depending on the ethnicity of tested groups

(Yogev et al., 2004). GDM recurrence during second pregnancy among American population amounted to 41.3%, whereas in pregnant women who have not suffered from GDM during their first pregnancy, the occurrence was 4.2% (Getahun, Fassett & Jacobsen, 2010).

Risk for stillbirth, aberrant fetal growth and various metabolic and electrolyte disturbances in fetuses of mothers with GDM is increased, as well as perinatal mortality (Ashwal & Hod, 2015). While the overall rate of macrosomia in non-diabetic population is 7-9%, in GDM population it is 20-45% (Mithanchez, 2010; Alberico et al., 2014). There is also an increased risk of neonatal hypoglycaemia (in 18% of newborns) (Ramos et al., 2012), neonatal hypocalcaemia, polycythaemia and hyperbilirubinaemia and neonatal respiratory distress (Ashwal & Hod, 2015). In the long term, these children have a higher risk of obesity, metabolic syndrome, T2DM and hypertension (Boney, Verma, Tucker & Vohr, 2005; Gabbay-Benziv & Baschat, 2014). Also, LGA newborns have a higher risk of developing metabolic syndrome and diabetes during childhood, adolescence and adulthood (Barker, 1994; Guerrero-Romero et al., 2010; Harder et al., 2009). GDM triggers and transmits health issues from one generation to the next.

## 2.2 Diagnosis of GDM

Different criteria are used for screening and diagnosis of GDM worldwide. Screening can be selective or universal, but by screening only the high risk population, up to 30% of women with GDM can be missed (Poomalar, 2015). In areas with low incidence of GDM (< 3%) selective screening could be acceptable, but if the prevalence is higher, universal screening is recommended (James et al., 2011).

International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel developed new diagnostic criteria for GDM (Metzger et al., 2010) based on the results of Hyperglycaemia and Pregnancy Adverse Outcome Study (HAPO), a multicenter study, which included 25505 pregnant women (Metzger et al., 2008). Pregnant women were tested with the oral glucose tolerance test (OGTT) and followed for adverse outcomes. Cut-off points were defined according to infant birth weight, cord blood C-peptide and neonatal body fat composition. These cut-off points indicated a 75% increased risk of adverse pregnancy outcomes

(Metzger et al., 2010). IADPSG criteria recommend universal or selective screening on the first antenatal visit and GDM is diagnosed if fasting plasma glucose (FPG) level is between 5.1 and 7.0 mmol/L. If FPG is ≥ 7.0 mmol/L, a diagnosis of overt diabetes is made. In all women previously not diagnosed with GDM, the two hour OGTT with 75g of glucose is performed between the 24th and the 28th week of pregnancy. GDM is diagnosed if there is one or more abnormal values: FPG ≥ 5.1 mmol/L, 1 h glucose ≥ 10.0 mmol/L, and 2 h glucose ≥ 8.5 mmol/L. If FPG is ≥ 7.0 mmol/L the diagnosis of overt diabetes mellitus is made. WHO (2013) accepted IADPSG criteria with one difference: instead of using the term "overt diabetes", WHO uses the term "diabetes mellitus in pregnancy". Based on IADPSG criteria, a rise in the incidence of GDM is expected, reaching 15-20% of all pregnancies (ADA, 2014). IADPSG criteria are also accepted by the Croatian Perinatology Society (Vucic Lovrencic et al., 2013).

## 2.3 Treatment of GDM

There are several benefits of treating even mild cases of GDM. Cochrane review confirms a reduction in the proportion of infants weighing more than 4 kg (RR=0.46 95%, CI: 0.34-0.63), infants weighing greater than 90th birth centile (RR=0.55, 95% CI: 0.30-0.99) and perinatal morbidity (RR=0.32, 95% CI: 0.14-0.73) in comparison with women receiving only routine antenatal care, but not intensive treatment for mild GDM (Alwan, Tuffnell & West, 2009).

The primary aim of treating GDM is to optimize glycaemic control and improve pregnancy outcomes (Alwan et al., 2009). Changes in diet and lifestyle are usually recommended as the primary therapeutic strategy to achieve acceptable glycaemic control (ACOG, 2012; National Institute for Health and Clinical Excellence (NICE), 2008). Glycaemic targets which should be achieved are capillary glucose concentrations of ≤ 5.3 mmol/L preprandially, ≤ 7.8 mmol/L 1 h post meal and ≤ 6.7 mmol/L 2 h post meal.

Recommended total daily dietary intake for underweight women with GDM (BMI < 19.8 kg/m$^2$) is 35-40 kcal/kg/day of the ideal body weight. For normal body weight women (BMI 19.8 – 29.9 kg/m$^2$), this should be 30-35 kcal/kg/day of the ideal body weight, and for overweight women (BMI ≥ 30 kg/m$^2$) 25-30 kcal/kg/day of

the ideal body weight (Poomalar, 2015). Their diet should consist of three meals per day and four snacks, because smaller and frequent meals lead to better satiety and compliance and reduce postprandial glucose peaks (Ashwall & Hod, 2015). Caloric intake of carbohydrates should be 33-40%, instead of 50-60%, with 20% of proteins and 40% of fat (ACOG, 2013). Food with low glycaemic index is recommended because it produces a better glucose control. Severe calorie restriction to < 1500 kcal/day is not recommended because it is associated with an increased incidence of ketonaemia which could potentially result in lowered mental developmental scores of the child (Rizzo, Metzger, Burns & Burns, 1991). ADA (2004) recommends a 30-33% restriction in caloric intake in obese women, but not lower than 1800 kcal/day.

If these measures fail to establish adequate glycaemic control within 1-2 weeks, pharmacological therapy is introduced. Approximatelly 15% of women with GDM do not succeed in meeting gylcaemic targets with diet and require pharmacological treatment (Aswhal & Hod, 2015). Insulin therapy is used primarily, whereas recently oral hypoglycaemic agents for GDM, such as metformin and glyburide, have started to be in use. Regarding the insulin therapy, short acting insulin (regular human insulin (RHI)) is used to prevent the glucose peak following a meal, and intermediate acting insulin (neutral protamine hagedorn (NPH)) for hepatic insulin production in the fasting state (Poomalar, 2015). There are also newer rapid acting insulin analogs, like insulin aspart and lispro, which can be used instead of short acting insulin because they start their action within 15 minutes, reach a peak by 31-70 min and act for 2-4 h (Poomalar, 2015). Also, newer long acting insulin analog detemir provides flatter profile with a more even distribution of metabolic effect in comparison to NPH, along with lower rates of hypoglycaemia (Korsatko et al., 2013).

However, recent guidelines suggest that oral medications are equivalent in efficacy with insulin and appropriate for first-line therapy (ACOG, 2013; National Collaborating Centre for Women's and Children's Health, 2015) with much simpler and patient-friendly administration. Metformin does not increase adverse maternal and neonatal outcomes in comparison with insulin and it is also associated with less weight gain and neonatal hypoglycaemia (Su & Wang, 2014). Also, there are no significant differences either in postprandial glucose level between women on oral medication and women on insulin therapy, or in rates of fetal macrosomia and

mean birth weight, and adverse maternal and neonatal outcomes (Dhulkotia, Ola, Fraser & Farrel, 2010; Nicholson et al., 2009).

Also, as a part of treatment, it is recommended to continue or initiate exercising with moderate intensity for all pregnant women without contraindications (NICE, 2008; ACOG, 2013; ADA 2015). However, available data on the effects of physical activity on GDM are based on a small number of trials and exercise is used as additional therapy exclusively. Randomized controlled trials dealing with optimal frequency, intensity, type and duration of physical activities are yet to be conducted in order to determine the exercise modality with the best results.

Poor glycaemic control increases the risk of fetal demise, and women on insulin therapy should be monitored more strictly. Antepartum fetal surveillance should be started from the 32nd week in pregnant women on pharmacological therapy and women should also monitor fetal movements during the last 8-10 weeks of the pregnancy (Poomalar, 2015). If there are associated comorbidities, intrauterine growth restriction or macrosomia, biophysical profile testing and Doppler velocimetry should be performed to assess umbilical blood flow. There is no consensus regarding antepartal testing of women with GDM which are well controlled with diet only (Poomalar, 2015). Regarding the timing of delivery, there is also no consensus. NICE (Walker, 2008) and ADA (2004) guidelines recommend labour induction after the 38th week of pregnancy, while ACOG (2013) does not recommend routine delivery before the 40th week if GDM is well controlled. On the other hand, Caesarean delivery is recommended only if estimated fetal weight exceeds 4500 g (Walker, 2008; Rouse, Owen, Goldenberg & Cliver, 1996).

# 3 PHYSICAL EXERCISE AND T2DM

T2DM is a global health problem. According to WHO, the number of people diagnosed with diabetes in the world has increased from 30 million in 1989 to 171 million in 2000 (WHO, 2006). Furthermore, rates of diabetes are expected to increase and WHO predicts that the worldwide prevalence in adults will reach 6.4% by 2030, which corresponds to a 39% increase from 2000 to 2030 (Wild, Roglic, Green, Sicree & King, 2004). Also, it is estimated that approximately 90-95% of diagnosed cases of diabetes will have T2DM (Harris, 1995). Incidence of T2DM has doubled over the last 30 years of the 20th century in the United States (Fox et al., 2006). Approximately 25% of people with T2DM do not have official medical diagnosis (Centers for Disease Control and Prevention, 2011).

T2DM is the sixth-leading cause of death, and most of these deaths are attributed to cardiovascular disease (Simpson, Corabian, Jacobs & Johnson, 2003; Gu, Cowie & Harris, 1998). Healthcare costs attributed to T2DM have been estimated to $172 billion in 2007 in the United States (Centers for Disease Control and Prevention, 2008) and are likely to rise due to cardiovascular complications (Mathers & Penm, 1999).

There are numerous benefits in preventing and treating T2DM. These include improvement of glycaemic control, body composition, cardiorespiratory fitness, cardiovascular risk, physical conditioning and well-being in patients with T2DM, prediabetes or individuals with risk factors (Marwick et al., 2009; Snowling & Hopkins, 2006). Lifestyle interventions, which mainly included exercise and nutritional interventions for pre-diabetic population, have been very successful in the prevention of T2DM (Hordern et al., 2012). U.S. Diabetes Prevention Program reported a 58% reduction in the incidence of T2DM from a four-year lifestyle intervention which included 150 min per week of moderate physical activity and dietary change designed to induce a -7% weight loss (Knowler et al., 2002). Increase in physical activity in the prediabetic individuals is twice as effective as metformin and standard medical care and reduces the likelihood of T2DM by 63-65% (Laaksonen et al., 2005). For each 1% of increase in the level of glycated haemoglobin (HbA1c), the relative risk of cardiovascular disease increases by 1.18% (Selvin et al., 2004). Furthermore, each -1% of decrease in HbA1c levels is associated with a -37% reduction in microvascular complications and a -14%

reduction in myocardial infarctions in patients with T2DM (UK Prospective Diabetes Study Group, 1998).

Individuals with diabetes are often physically inactive and live a sedentary lifestyle (Church, Lamonte, Barlow & Blair, 2005; Zhao, Ford, Li & Mokdad, 2008; Larose et al., 2011). Even small amounts of exercise can positively affect markers of glucose and fat metabolism in previously sedentary individuals (Duncan et al., 2003). Exercise leads to improvements in metabolic control, measured by HbA1c, blood glucose level and insulin sensitivity (Marwick et al., 2009). Muscle contractions can elicit movement of GLUT4 glucose transporter to the plasma membrane independently of insulin (Ploug & Ralston, 2002). Hypertrophy of the muscle and increase in skeletal muscle mass caused by exercise are also associated with a decline in HbA1c, which is probably related to increased glycogen and glucose within the muscle (Eves & Plotnikoff, 2006). Moderate intensity exercise increases adiponectin levels (Brooks et al., 2007), which has insulin sensitizing, anti-inflammatory and anti-atherogenic role by direct reciprocal inhibition of TNF-α (Simpson & Fiatarone Singh, 2008). This is followed by a decline in C-reactive protein levels and also decreased resistin, interleukin-6, interleukin-18 and other inflammatory markers (Brooks et al., 2007; Kadoglou et al., 2007; Ostergard et al., 2006).

Almost any type of physical activity improves glucose uptake and insulin sensitivity by enhancing resting insulin action and lowering blood glucose for 2-72h after the last session of activity, depending on the duration and intensity of exercise and subsequent food ingestion (King et al., 1995; Boulé, Haddad, Kenny, Wells & Sigal, 2001; O'Gorman et al., 2006). Muscular uptake of blood glucose during moderate exercise exceeds hepatic glucose production, which causes a decline of blood glucose levels during the activity (Minuk, Vranic, Hanna, Albisser & Zinman, 1981). This causes a further decline in plasma insulin levels, which reduces the risk of exercise-induced hypoglycaemia as long as the individual does not take insulin (Koivisto & Defronzo, 1983).

Only 20 minutes of self-paced walking after dinner is effective at lowering its glycaemic impact in comparison with pre-meal walking or no exercise (Coldberg et al., 2009). A single bout of either 30 min of moderate aerobic exercise or 45 min of moderate resistance training reduces the prevalence of hyperglycaemia for the following 24 h (van Dijk et al., 2012). Physical activity of any intensity enhances

the uptake of circulating glucose for glycogen synthesis (Christ-Roberts et al., 2003; Galbo, Tobin & van Loon, 2007), but more prolonged or intense activity usually enhances acute insulin action for a longer period of time (Houmard et al., 2004; Sigal et al., 2007). Low-volume, high-intensity training (HIT) rapidly improves glucose control and induces adaptations in skeletal muscle which consequently improve metabolic health in individuals with T2DM (Little et al., 2011). However, when matched for energy cost, prolonged, continuous low- to moderate-intensity aerobic exercise and moderate- to high-intensity training done 3 days per week are equally effective in lowering HbA1c and increasing the whole body and skeletal muscle oxidative capacity in obese individuals with T2DM (Hansen et al., 2009).

Resistance exercise also improves glucose tolerance, but has also some additional metabolic benefits (Coldberg, 2012). Regular resistance exercise improves overall glycaemic control and insulin sensitivity by increasing levels of muscle GLUT4, insulin receptors, protein kinase B, glycogen synthase, and glycogen synthase total activity following acute training (Holten et al., 2004). Sixteen weeks of progressive resistance training not only significantly reduces HbA1c levels in individuals with T2DM, but also increases muscle glycogen stores and allows reducing prescribed medication dosages in 72% of participants (Castaneda et al., 2002).

Both aerobic and resistance exercise or a combination of them has shown beneficial effects. The combination of both modes of training has synergistic effects (Sigal et al., 2007) and it seems to show better results than each mode of exercise alone (Church et al., 2010). The study which examined the effects of equal energy expenditure among combined and separate aerobic and resistance training groups revealed that only those in the combined training group improved their HbA1c levels significantly (Church et al., 2010). Combined aerobic and resistance exercise, as well as aerobic exercise alone, performed at least two times per week at an intensity of 60-85% of maximal heart rate, is associated with a significant decline in HbA1c, triglyceride levels, waist circumference and systolic blood pressure in individuals with T2DM (Chudyk & Petrella, 2011).

Studies which showed no improvements in glycaemic control have reported poor exercise compliance, low exercise volume and/or intensity (Krousel-Wood et al., 2008; Brun et al., 2008; Khan & Rupp, 1995).

Exercise recommendations for individuals with T2DM are similar to those for healthy population (Haskell et al., 2007). Patients should exercise for a minimum of 210 min of moderate intensity or 125 min of vigorous intensity per week. Endurance and resistance exercise should be combined in one session, and it is recommended to perform at least two or more sessions of resistance exercises per week (2-4 sets of 8-10 repetitions). Exercise should be performed at least three times a week, and there should be no more than two consecutive days without exercise because insulin sensitivity declines markedly by 48 h post exercise (Borghouts & Keizer, 2000). Intensity of exercise should be a combination of moderate and vigorious exercise, if there are no contraindications for vigorous exercise. The risks associated with exercise are considered less than the risks of staying inactive, even in older adults with multiple comorbidities (Hordern et al., 2012).

# 4 EXERCISE AND GDM

Benefits of exercise and physical activity in prevention and treatment of T2DM are well known (Haskell et al., 2007). Exercise therapy is proven, although under-recognised, in the prevention and management of T2DM (Marwick et al., 2009). The Canadian Diabetes Association encourages physical activity for diabetic pregnant women with the frequency, type, duration and intensity tailored to the individual obstetric risk (2003). Furthermore, ADA, as well as ACOG, recommends an exercise programme as a part of the treatment of GDM (ADA, 2015; ACOG 2001).

## 4.1 The role of exercise in prevention of GDM

Impacts of exercise before and during pregnancy on the prevention of GDM are reported mainly in cohort studies and a small number of randomized controlled trials, with contradictory results. Trials corelate higher levels of physical activity before and during early pregnancy with lower risk of developing GDM (Tobias, Zhang, van Dam, Bowers & Hu, 2011). There has been only one randomized trial on the effects of exercise on the prevention of GDM and insulin resistance in the general population of healthy pregnant women (Stafne, Salvensen, Romundstad, Eggebø, Carlsen & Mørkved, 2012b). Another two randomized controlled trials have studied the impact of exercise in healthy pregnant women on glycaemic control parameters (insulin resistance, blood glucose and insulin levels) (Hopkins, Baldi, Cutfield, McGowan & Hofman, 2010; Callaway et al., 2010). Unfortunately, the samples were small and did not have sufficient statistical power to measure GDM prevalence as an outcome.

Stafne et al., (2012b) performed a randomized controlled trial which included 855 healthy women whose duration of pregnancy ranged from 18 to 22 weeks. The experimental group exercised during 12 weeks and the control group received only standard antenatal healthcare. The exercise programme consisted of a combination of moderate and high-intensity exercises for three or more days a week and included aerobic, strength and balance exercises. Supervised exercise sessions which lasted 60 minutes were performed once per week. Furthermore, women were instructed to perform a home exercise programme, which consisted of 30 minutes

of endurance exercises and 15 minutes of strength and balance exercises, at least twice a week. The main outcomes of research were the occurence of gestational diabetes and insulin resistance. There were no statistically significant differences in GDM prevalence between the 32nd and the 36th week of pregnancy between groups (25/375 (7%) for the experimental group vs 18/327 (6%) for the control group, P = 0.52). Furthermore, there were no statistically significant differences in insulin resistance. Only 55% of women in the experimental group were succesful in following the recommended exercise protocol. However, pregnant women in the intervention group managed to exercise approximately twice per week and only 10% of pregnant women from the control group exercised three times per week. Their average exercise frequency was 0.7 days per week. Pregnancy outcomes were similar for both groups, but the 12-week exercise programme did not prevent gestational diabetes nor improved insulin resistance.

Another randomized controlled trial researching the effects of aerobic exercise programme on maternal insulin sensitivity and neonatal outcomes in 84 healthy pregnant women during their second half of pregnancy was performed by Hopkins et al. (2010). The experimental group was instructed to use stationary bicycle from their 20th gestational week until birth. The maximum frequency of training sessions was up to five 40-minutes training sessions per week. Exercise intensity was targeted to approximately 65% of maximal oxygen uptake ($VO_2$max). Adherence to exercise protocol was 75±17%. There was a significant statistical difference in the birth weight and BMI of infants, but no significant differences in maternal insulin sensitivity. The exercise group's infants had lower birth weight (P = 0.03) and their BMI was lower after birth (P = 0.04).

The purpose of the trial which included 50 pregnant women, performed by Callaway et al. (2010), was to examine the feasibility of exercise programmes which aim to prevent GDM in obese women. They reported that 73% of women in the exercise group successfully burned more than 900 kcal per week in comparison with 42% of women in the non intervention group (P = 0.047). Also, the women in the experimental group had lower levels of fasting glucose in the 28th week of pregnancy (P = 0.03) and insulin levels in the 36th week of pregnancy (P = 0.05). There was no significant difference in insulin resistance measured by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The authors concluded that these findings were due to potentially insufficient differences in exercise levels between the two groups and that exercise levels were not sufficient to improve

insulin resistance. Also, they concluded that HOMA-IR might not be the best test for researching the effect of exercise on insulin resistence. Exercise probably reduces peripheral insulin resistance, while HOMA-IR provides better insight on hepatic insulin resistance.

Redden, Lamonte, Freudenheim & Rudra (2011) researched the relation between recreational physical activity before pregnancy and GDM. Their cross-sectional study included 1051 women with GDM and 10351 women who did not develop GDM. Women who exercised more than five times per week had 31% less chance for GDM (aOR 0.69, 95% CI 0.46-1.03) in comparison with women who exercised less than twice per week. Also, 1-4 sessions of exercising per week lowered the chance of GDM for 7% (aOR 0.93, 95% CI 0.72-1.19). Similar results were reported in prospective cohort studies indicating that the risk of GDM is decreased by 20-55% if women exercise before and during the pregnancy (Dempsey et al., 2004; Oken et al., 2006; Zhang, Solomon, Manson & Hu, 2006). There is a 55% decreased risk of GDM in the group of most active women before pregnancy, those in the highest quintile of physical activity (PA) levels (OR 0.45, 95% CI 0.28-0.75, P=0.002) in comparison with the women in lower quintiles (Tobias et al., 2011). Also, there is a -24% decreased risk of GDM in the group of women who were most active during their early pregnancy (OR 0.76, 95% CI 0.70-0.83, P < 0.001) (Tobias et al., 2011).

Zhant et al. (2006) studied the relation between quantity, type and intensity of exercise and lifestyle before pregnancy and the risk of developing GDM. The results showed a significant inverse relation between strenuous physical activity and the risk of GDM. Furthermore, even women who used to power walk had a markedly lower risk compared to those who took slower walks.

Watching television for 20 or more hours per week and not engaging in vigorous physical activity substantially increases the risk of GDM as opposed to watching television for less than 2 hours per week and being physically active (RR 2.30, 95% CI 1.06-4.97).

Walking before pregnancy is also inversely correlated with the risk of GDM. Women who had the habit of long-distance power walking for > 2 miles a day (Dempsey et al., 2004), or > 30 minutes a day (Zhang et al., 2006) had decreased chances of developing GDM in comparison with women who were less active. Likewise, stair

climbing before and during the early period of pregnancy (≥ 10-15 flights of stairs a day) is inversely related to the risk of developing GDM (Dempsey et al., 2004; Zhang et al., 2006).

Even those women who had been previously inactive, but began to exercise after conception have a lower risk of GDM. Liu, Laditka, Mayer-Davis & Pate (2008) analysed 4813 physically inactive women who gave birth to one child and had not been previously diagnosed with diabetes. Women who started exercising in pregnancy (11.8%) had a 57% lower adjusted risk of GDM in comparison with those who remained inactive (OR 0.43, 95% CI 0.20-0.93). Even low-intensity exercise in combination with diet reduces the risk of GDM and regulates blood glucose levels. Sopper, Hammond, Giroux, McManus & Mottola (2004) developed the prevention programme designed for women at high risk of GDM (NELIP - *Nutrition and Exercise Lifestyle Intervention Program*). It consists of slow walks (30% $VO_2$max) combined with diet (1995 kcal a day, with a maximum of 200 g carbohydrates a day). Pregnant women who participated in it did not develop GDM. Also, exaggerated increase of BMI was prevented and glucose tolerance was normal for two months postpartum. Insulin sensitivity index in high risk women in the programme remained similar to women with low risk for GDM (Batada et al., 2003).

Exercise also prevents excessive weight gain during pregnancy, thus indirectly preventing GDM. Unfortunately, only approximately 50% of non-pregnant women are physically active according to recommendations and this percentage further drops after they concieve (Bauman, Ford & Armstrong, 2001). It is very likely that regular exercise significantly reduces GDM prevalence, but for best results, exercise must be regular (Coldberg et al., 2010). Exercising before and during the early period of pregnancy could be more influental for GDM prevention than exercise in late pregnancy, which is problably the consequence of chronic adaptations related to glucose uptake in skeletal muscles and better tolerance of metabolic stress in pregnancy. Additional trials are required to determine optimal frequency, intensity, type and duration of exercise for the prevention of GDM.

## 4.2 Role of exercise in the treatment of GDM

While the use of exercise in the treatment of T2DM is supported by plenty of evidence, there is limited evidence on the effects of exercise on the course and outcomes of GDM. Only nine prospective trials on this subject were performed (Table 1), seven of which were randomized controlled trials (Jovanovic-Peterson, Durak & Peterson, 1989; Bung, Artal, Khodiguian & Kjos, 1991; Avery, Leon & Kopher, 1997; Brankston, Mitchell, Ryan & Okun, 2004; de Barros, Lopes, Francisco, Sapienza & Zugaib, 2010; Bo et al., 2014; Halse, Wallman, Newnham & Guelfi, 2015) and two non-randomized (Artal, Catanzaro, Gavard, Mostello & Friganza, 2007; Davenport, Mottola, McManus & Gratton, 2008). Seven of these trials examined the effects of aerobic exercise programmes (Jovanovic-Peterson et al., 1989; Bung et al., 1991; Avery et al., 1997; Artal et al., 2007; Davenport et al., 2008; Bo et al., 2014; Halse et al., 2015), whereas only two examined the role of resistance exercise (Brankston et al., 2004; de Barros et al., 2010). None of the trials examined the effect of combined aerobic and resistance exercise.

Measured outcomes consisted of pregnancy and perinatal complications and outcomes, glycaemic control parameters (fasting glucose levels and levels after oral glucose ingestion, HbA1c, and succes of mantaining glucose level within recommended values) and the need for insulin therapy. Not all trials measured the same outcomes, making it difficult to compare results.

A total of 544 pregnant women were included in these trials, 418 within randomized trials. Exercise programmes were conducted mostly during the third trimester, with the interventions lasting approximately six weeks. The exercise programmes were mostly implemented three times a week with the duration of 20-45 minutes. The type, frequency, intensity and duration of the programmes varied between trials. All trials included only pregnant women with GDM, while excluding pregnant women with type 1 or 2 diabetes. Regardless of different methodologies and small samples, in most trials there was a statistically significant difference in glycaemic control or the need for insulin therapy (Jovanovic-Peterson et al., 1989; Brankston et al., 2004; Bung et al., 1991; Davenport et al., 2008; de Barros et al., 2010; Bo et al., 2014; Halse et al., 2015).

A programme comprised of six weeks of twenty minute workout sessions three times a week, with the intensity lower or equal to 50% $VO_2$max, which is significantly lower than currently recommended for diabetic and gravid population (American Diabetic Association, 2015; ACOG, 2001; ACOG, 2002) significantly decreased the levels of glycated haemoglobin, fasting glucose and the plasma glucose level one hour after oral glucose ingestion in pregnant women with GDM (Jovanovic-Peterson et al., 1989). Similarly, 8 weeks of a more demanding exercise programme consisting of riding a stationary bicycle with the intensity of 50% $VO_2$max and the duration of 45 minutes performed three times a week has similar effects as insulin therapy regarding the maintainance of euglycaemia and the rate of maternal and neonatal complications (Bung et al., 1991).

Likewise, structured low-intensity (30% of heart rate reserve) walking protocol performed 3-4 times a week for at least 6 weeks in pregnant women with GDM significantly influenced fasting and postprandial glucose levels and dosage of insulin units per day (Davenport et al., 2008). Brisk walking at least 20 min per day every day from the 24th-26th until the 38th week of pregnancy, besides reducing postprandial glucose, HbA1c, C-reactive protein and triglyceride levels, also reduces any maternal and neonatal complications (Bo et al., 2014).

A more intensive cycling programme (moderate-intensity, 65-75% of maximal heart rate (HRmax), with intervals of varying intensities, 55-85% HRmax) performed 3 times per week in combination with two unsupervised exercise sessions for 6 weeks also lowered mean daily postprandial glucose concentrations compared to the control group, despite consuming greater proportion of dietary carbohydrate in the exercise group (Halse et al., 2015). However, there were no differences between groups in HbA1c values or glucose and insulin response to oral glucose ingestion post-intervention.

On the other hand, Avery et al. (1997) failed to confirm these results, as they did not find any statistically significant differences between the experimental and the control group with respect to HbA1c, the need for insulin therapy, fasting glucose levels, and levels after oral glucose ingestion. The programme was a combination of supervised exercise using stationary bicycle twice a week, with the intensity of approximately 70% of maximum heart rate, for 30 minutes, and additional home exercise twice a week for 30 minutes. However, less than 25% of subjects from the experimental group completed the study.

Artal et al. (2007) performed a trial on a sample of 96 pregnant women. Subjects were not randomly allocated to the experimental group, but rather voluntarily chose whether to participate in the experimental group using dietary therapy and exercise seven days a week (N=39), or the control group (N=57), using solely diet. The authors concluded that the need for insulin therapy was similar between the two groups, however, with a significantly lower maternal body mass increase in the experimental group.

There were only two trials on the effect of resistance exercises. Brankston et al. (2004) did not find any significant difference in the number of pregnant women who required insulin therapy, but pregnant women who exercised required lower dosage of insulin and it was introduced later in the pregnancy. The exercise programme involved circuit training, using resistance bands throughout eight exercises, with intensity level of 12-15 on rating of the perceived exertion (RPE) scale, three times a week. Both groups received dietary counselling. However, this trial was conducted on a small sample (n=32), with significant differences in pre-pregnancy body weight and hyperglycaemia levels between the experimental and control groups.

Contrary to this, another trial on 64 pregnant women with GDM examined the impact of resistance exercises with elastic bands on the need for insulin therapy and glucose levels (de Barros et al., 2010). The exercise group displayed statistically significant differences in insulin use and was more successful in maintaining glucose levels within recommended values. The exercise programme involved circuit training using resistance bands for all major muscle groups. Exercises were performed once a week under supervision, and additionally two times per week at home.

*Table 1: Characteristics of prospective trials on the role of exercise in the treatment of GDM.*

| Authors | Sample | R | Intervention | Outcome measures and results |
|---|---|---|---|---|
| Jovanovic-Peterson et al., 1989 | 19 pregnant women with GDM | Yes | EG (n=10): 6 weeks of dietary therapy with 24-30 kcal/kg per day and 20 minutes of exercise using upper-body ergometer 3x a week<br>CG (n=9): dietary therapy without exercise | Fasting glucose levels: decreased ($P < 0.001$);<br>Postprandial glucose levels: decreased ($P < 0,01$);<br>Glucose levels 1h after oral intestion (OGTT): decreased ($P < 0.001$);<br>HbA1c: decreased ($P < 0.001$) |
| Bung et al., 1991 | 34 pregnant women prior to 33rd week of pregnancy, with GDM | Yes | EG (n=17): diet (30 kcal/kg per day) + exercise on bicycle 45 min 3x a week at 50% $VO_2$ max<br>CG (n=17): diet (30 kcal/kg per day) + insulin therapy | Weekly blood glucose levels: no difference;<br>Newborn weight and neonatal hypoglycaemia:<br>no difference;<br>Cesarean section, vacuum or forceps mode of delivery: no difference |

| | | | | |
|---|---|---|---|---|
| Avery et al., 1997 | 29 pregnant women at 34th week of pregnancy or earlier, with GDM | Yes | EG (n=15): 30 minutes of exercise 3-4 times a week: cycle ergometer exercise at cca 70% max heart rate frequency 2x a week under supervision + 30 min exercise 2x a week at home + dietary counselling<br>CG (n=14): usual level of physical activity + dietary counselling | Fasting glucose level: no difference (P = 0.80);<br>Postprandial glucose levels: no difference (P = 0.10; P = 0.40; P = 0.10);<br>HbA1c: no difference (P = 0.26);<br>Insulin treatment: no difference (P = 0.65)<br>Newborn birth weight, hypoglycaemia in newborns and Apgar scores: no difference (P = 0.30; P = 0.74; P = 0.88);<br>Maternal weight at study end: no difference (P = 0.53) |
| Brankston et al., 2004 | 32 pregnant women between 26th and 32nd week, with GDM | Yes | EG (n=16): circuit training consisting of 8 exercises, RPE 12-14, 3x a week + dietary counselling<br>CG (n=16): requested not to initiate the specific exercise program + dietary counselling | Fasting glucose: no difference (P = 0.07);<br>Postprandial glucose: decreased (P < 0.05);<br>Insulin treatment: no difference (P = 0.48);<br>Amount of insulin required: decreased (P < 0.05);<br>Latency to insulin requirement: decreased (P < 0.05) |
| Artal et al., 2007 | 96 pregnant women with GDM before 33rd week of pregnancy | No | EG (n=39): dietary therapy and exercise at 60% $VO_2$max<br>CG (n=57): dietary therapy | Total weight gain and average weight gain per week: decreased (P < 0.05; P < 0.01);<br>Newborn weight: no difference (P =0.64);<br>Cesarean section rate: no difference (P = 0.80) |

| | | | | |
|---|---|---|---|---|
| Davenport et al., 2008 | 30 pregnant women with GDM already on insulin therapy | No | EG (n=10): walking program 3-4x a week at 30% HRR (at least 6 weeks) + dietary counselling<br>CG (n=20): conventional management + dietary counselling | Fasting glucose: decreased ($P < 0.05$);<br>Postprandial glucose: decreased ($P < 0.05$);<br>Insulin units per day: fewer ($P < 0.05$);<br>Weight gain: no difference ($P > 0.05$);<br>Gestational age, newborn weight and macrosomia: no difference ($P > 0.05$);<br>Cesarean section rate: no difference ($P > 0.05$) |
| de Barros et al., 2010 | 64 pregnant women with GDM, between 24th and 34th week till the end of pregnancy | Yes | EG (n=32): circuit training using resistance exercise with resistance bands for the major muscle groups 3x a week for 30-40 min, 8 stations, 15 repetitions, 0.5-1 min pauses, 2-3 intervals<br>CG (n=32): dietary therapy | Insulin treatment: decreased ($P = 0.05$);<br>Amount of insulin required and latency to insulin requirement: no difference ($P = 0.401$; $P = 0.715$);<br>Mean fasting glucose level: no difference ($P = 0.112$);<br>Mean postprandial glucose level: no difference ($P = 0.084$);<br>Percentage of weeks spent within target glucose range: increased ($P = 0.006$);<br>Cesarean sections: no difference ($P = 0.412$);<br>Delivery BMI and pregnancy weight gain: no difference ($P = 0.600$; $P = 0.324$);<br>Gestational age at delivery and newborn weight: no difference ($P = 0.883$; $P = 9.531$) |

| | | | | |
|---|---|---|---|---|
| Bo et al., 2014 | 200 pregnant women with GDM, from 24-26th week to 38th week or before delivery | Yes | EG (99): brisk walk at least 20 min per day at Borg's scale target rating 12-14<br>CG (101): dietary recommendation with or without behavioural dietary recommendations | Fasting glucose level: no difference (P = 0.13);<br>Postprandial glucose level: decreased (P < 0.001);<br>HbA1c: decreased (P < 0.001);<br>Total cholesterol, HDL cholesterol, triglyceride levels: no difference in total cholesterol and HDL cholesterol (P = 0.42; P = 0.74), lower triglyceride level( P = 0.02);<br>Fasting insulin: no difference (P = 0.86);<br>HOMA-IR: no difference (P = 0.79);<br>C-reactive protein: decreased (P < 0.001);<br>Insulin treatment: no difference (P = 0.77);<br>Maternal/neonatal complications: decreased (P = 0.02);<br>Maternal weight and BMI: no difference (P = 0.16; P = 0.22) |

| | | | | |
|---|---|---|---|---|
| Halse et al., 2015 | 40 pregnant women within 1 week of GDM diagnosis, from 28.8 ± 0.9 week until 34th week of pregnancy | Yes | EG (n = 20): combination of supervised home based exercise training on an upright cycle ergometer 3x a week and unsupervised exercise 2x a week for 25-45 min for 6 ± 1 weeks; moderate-intensity cycling (65-75% age-predicted HRmax) in combination with higher (75-85% age-predicted HRmax) and lower (55-65% age-predicted HRmax) intensity bouts<br>CG (n = 20): conventional management | Pre- and post exercise:<br>Blood glucose level: decreased ($P < 0.001$)<br>During intervention:<br>Daily fasting glucose level: no difference ($P = 0.083$);<br>Daily postprandial glucose level: decreased ($P = 0.046$)<br>Post-intervention:<br>Blood glucose and insulin response to 75 g OGTT: no difference ($P > 0.05$);<br>HbA1c: no difference ($P > 0.05$) |

*R – randomization; EG – experimental group; CG – control group; n – sample size; HRR – heart rate reserve; HRmax – maximal heart rate; RPE – rate of perceived exertion; GDM – gestational diabetes mellitus; BMI – body mass index; HOMA-IR – homeostasis model assessment of insulin resistance.*

# 5 AIM OF THE THESIS

The aim of this doctoral thesis was to examine and add new scientific evidence on possible health-related effects of the application of supervised individualised structured physical exercise programme consisting of aerobic and resistance exercises on the course and outcomes of gestational diabetes mellitus. The primary goal of research was to investigate how this exercise programme affects the course and outcomes of pregnancy complicated by GDM. Specific goals were to gather and analyse data on:

- glycaemic control of the pregnant women,
- rate of complications during pregnancy,
- weight gain and body fat percentage changes during pregnancy,
- rate of complications and mode of delivery and
- health status and weight of the newborn.

## 5.1 Hypotheses

The main hypothesis of this dissertation is that participation in a structured programme of exercise significantly impacts parameters of glycaemic control and the course of GDM, complications during pregnancy, labour and delivery, as well as birth outcomes, i.e. there are significant statistical differences between the experimental group of women who exercised and those in the control group who received only standard medical care. The following specific hypotheses were developed based on the objectives of the trial:

H1: There will be a significant statistical differences regarding parameters of glycaemic control between the pregnant women who participated in a structured exercise programme and those who received only standard medical care

$H1_1$: Pregnant women who participated in the exercise programme will have less need for pharmacological therapy for GDM (insulin and oral hypoglycaemic agents)

$H1_2$: Pregnant women who participated in the exercise programme will have lower levels of fasting glucose at the end of pregnancy

$H1_3$ Pregnant women who participated in the exercise programme will have lower levels of postprandial glucose at the end of pregnancy

H2 There will be a significant statistical difference regarding the rate of complications in pregnancy between pregnant women who participated in structured exercise programme and those who received only standard medical care

$H2_1$ Pregnant women who participated in the exercise programme will have a lower rate of pregnancy induced hypertension

$H2_2$ Pregnant women who participated in the exercise programme will have a lower rate of preeclampsia

$H2_3$ Pregnant women who participated in the exercise programme will have a lower rate of other serious complications in pregnancy

H3 There will be a significant statistical differences regarding the weight gain and fat mass gain in pregnancy between pregnant women who participated in the structured exercise programme and those who received only standard medical care

$H3_1$ Pregnant women who participated in the exercise programme will gain less body mass until labour than those who did not participate

$H3_2$ Pregnant women who participated in the exercise programme will gain less body fat until labour than those who did not participate

H4 There will be a significant statistical difference regarding the rate of complications during labour and delivery between pregnant women who participated in the structured exercise programme and those who received only standard medical care

$H4_1$ Pregnant women who participated in the exercise programme will have lower rates of prolonged labour than those who did not participate

$H4_2$ Pregnant women who participated in the exercise programme will have lower rates of labour induction than those who did not participate

$H4_3$ Pregnant women who participated in the exercise programme will have lower rates of vaginal instrumental delivery than those who did not participate

$H4_4$ Pregnant women who participated in the exercise programme will have lower rates of Caesarean section than those who did not participate

H5 There will be a significant statistical difference regarding the newborn's neonatal parameters and body mass between the pregnant women who participated in the structured exercise programme and those who received only standard medical care

$H5_1$ Newborns of women who participated in the exercise programme will have better Apgar scores than newborns of women who did not participate

$H5_2$ Newborns of women who participated in the exercise programme will have lower rates of perinatal and postnatal complications than newborns of women who did not participate.

$H5_3$ Newborns of women who participated in the exercise programme will have lower body mass than newborns of women who did not participate

$H5_4$ Newborns of women who participated in the exercise programme will have lower values of neonatal ponderal index than newborns of women who did not participate.

$H5_5$ Newborns of women who participated in the exercise programme will have lower values of body mass index than newborns of women who did not participate.

# 6 METHODS AND MATERIALS

## 6.1 Study design and ethics

The study was designed as randomized controlled trial (pretest-posttest randomized-groups design). Participants were randomized by block randomization web-based computerized procedure in two groups, experimental and control (Sealed Envelope Ltd, 2013). The staff involved with exercise sessions and assessments had no influence on the randomization procedure. Because of its nature, the study was not blinded.

Research was conducted under the Croatian national scientific project Diabetes and Metabolic Syndrome after Previous Gestational Diabetes (no. 108-1080408-0385) led by Professor Marina Ivanišević, MD, PhD. Ethical approval was obtained from University Hospital Centre Zagreb, Department of Gynaecology and Obstetrics of the University Hospital Centre Zagreb and University Hospital Merkur (Appendices 1-3). Written informed consent was obtained from every participant. Trial was conducted according to Good Clinical Practice, Declaration of Helsinki and positive legislature on patient's rights. Patient confidentiality was protected.

## 6.2 Participants

Pregnant women from the capital of Croatia and its surroundings diagnosed with GDM were potential participants in this trial. Participants were recruited by direct contact at two large hospitals, the Referral Centre for Diabetes in Pregnancy, Department of Gynaecology and Obstetrics, University Hospital Centre Zagreb and Referral Centre for Diabetes, University Clinic for Diabetes, Endocrinology and Metabolic Diseases Vuk Vrhovac, University Hospital Merkur in Zagreb, Croatia after they received their laboratory confirmation of GDM. IADPSG criteria for the diagnosis of GDM have been used (Metzger et al., 2010). The aim and implications of the study were briefly explained at the first contact and an information leaflet was given to women who expressed interest in the trial. Interested women contacted the principal investigator if they decided that they wanted to participate in the trial and a formal interview was scheduled to give them detailed information

about the trial, check eligibility criteria in detail, give them the information pack and obtain consent form.

Baseline participants' characteristics are shown in Table 2. All data are presented as means±standard deviation.

*Table 2: Baseline characteristics for the experimental and control groups.*

| Variable | EG (N = 18) | CG (N = 20) | P |
|---|---|---|---|
| Maternal age (years; mean ± SD) | 32.78 ± 3.83 | 31.95 ± 4.91 | 0.478 |
| Body height (m; mean ± SD) | 1.67 ± 0.07 | 1.68 ± 0.06 | 0.762 |
| Pre-pregnancy body mass (kg; mean ± SD) | 68.03 ± 13.65 | 71.60 ± 15.48 | 0.515 |
| Pre-pregnancy BMI in ($kg/m^2$; mean ± SD) | 24.39 ± 4.89 | 25.29 ± 4.65 | 0.515 |
| Gestational age at diagnosis (week; mean ± SD) | 22.44 ± 6.55 | 20.80 ± 6.05 | 0.409 |
| Parity (mean ± SD) | 0.72 ± 0.83 | 0.85 ± 0.99 | 0.806 |
| 75 g OGTT (mmol/L; mean ± SD) | | | |
| Fasting | 5.20 ± 0.39 | 5.10 ± 0.38 | 0.515 |
| 1h | 9.62 ± 2.14 | 8.57 ± 2.21 | 0.219 |
| 2h | 7.29 ± 2.26 | 7.08 ± 1.67 | 0.696 |
| Education | | | 0.851 |
| Secondary level (N; (%)) | 7 (38.89) | 7 (35.00) | |
| Tertiary level (N; (%)) | 11 (61.11) | 13 (65.00) | |
| Pre-pregnancy regular physical activity (N; (%)) | 9 (50.00) | 15 (75.00) | 0.196 |
| Positive family history of diabetes mellitus (N; (%)) | 7 (38.89) | 8 (40.00) | 0.965 |
| Total activity (MET-h*$week^{-1}$; mean ± SD) | 158.22±74.54 | 126.11±44.63 | 0.128 |
| Total activity of light intensity and above (≥ 1.5 METs) (MET-h*$week^{-1}$; mean ± SD) | 133.06±74.83 | 101.75±43.40 | 0.108 |

| | | | |
|---|---|---|---|
| By intensity of activity | | | |
| Sedentary (< 1.5 METs) (MET-h*week$^{-1}$; mean ± SD) | 25.16±13.82 | 24.36±17.09 | 0.696 |
| Light (1.5 – 2.9 METs) (MET-h*week$^{-1}$; mean ± SD) | 100.22±46.40 | 78.44±30.09 | 0.167 |
| Moderate (3.0 – 5.9 METs) (MET-h*week$^{-1}$; mean ± SD) | 32.69±43.70 | 22.92±22.35 | 0.696 |
| Vigorous (≥ 6.0 METs) (MET-h*week$^{-1}$; mean ± SD) | 0.17±0.33 | 0.40±0.76 | 0.478 |
| By type of activity | | | |
| Household/caregiving (MET-h*week$^{-1}$; mean ± SD) | 84.90±71.59 | 63.58±39.90 | 0.264 |
| Occupational (MET-h*week$^{-1}$; mean ± SD) | 19.41±30.69 | 6.90±21.25 | 0.085 |
| Sport/exercise (MET-h*week$^{-1}$; mean ± SD) | 3.15±1.98 | 2.15±2.18 | 0.061 |
| Transportation activity (MET-h*week$^{-1}$; mean ± SD) | 15.65±6.08 | 17.86±11.60 | 0.930 |
| Inactivity (MET-h*week$^{-1}$; mean ± SD) | 35.10±16.90 | 35.61±23.53 | 0.640 |

*EG – experimental group; CG – control group; N – sample size; BMI – body mass index; OGTT – oral glucose tolerance test; MET – metabolic equivalent.*

Inclusion criteria were an established diagnosis of gestational diabetes according to IADPSG criteria, age between 20 and 40, and the ability to read, understand and speak the Croatian language. We chose to include pregnant women in this age range because 93.8% of all births in Croatia happen then and also for easier comparison with previous trials (Rodin, 2013).

The upper limit for gestational age was set at 30 weeks at the time of inclusion to allow the minimum of exercise period of 6 weeks, until at least the 36th week of pregnancy. Exclusion criteria were medical history of diabetes and miscarriages, pharmacological treatment with oral hypoglycaemic agents and/or insulin

introduced prior the enrollment in the trial, existing comorbidities and contraindications for exercise according to ACOG (2002) criteria. Furthermore, pregnant women unable to attend exercise sessions were ineligible.

## 6.3 Assessments and measurements

Baseline information, which was taken at the initial interview, included taking demographic data, medical history including obstetric history, data regarding current pregnancy, family history of diabetes, lifestyle habits and physical activity levels, existence of contraindications for exercise, height, weight at the start of the pregnancy, results of the OGTT and review of their medical chart. Pregnant women randomized in the experimental group were scheduled for their first exercise session, and women from the control group were not seen until the 30th week of pregnancy where the next assessment was performed for the whole sample. In the 30th week, anthropological measurements were performed and physical activity levels assessed by a specific questionnaire. A review of medical chart was done to assess the course of pregnancy and glycaemic control. In the 33rd week only anthropological measurements were taken and in the 36th week we repeated all measurements and assessments performed in the 30th week of the pregnancy. After childbirth, the final interview was scheduled to gather the data on glycaemic control during the final weeks of pregnancy, the course of labour and delivery, neonatal health status, and anthropological data. Data were extracted from medical charts and hospital discharge letters.

### 6.3.1 Anthropological measurements

Anthropological measurements were taken in pregnancy week 30, 33 and 36. All anthropometric measurements were performed by the independent blinded physiotherapist. These included body mass, arm circumference and skinfold thickness. Body mass was taken with medical grade digital scale measuring to the nearest 0.1 kg (Body Composition Monitor BF511, Omron Healtcare, Kyoto, Japan). Body mass index was calculated according to the standard equation [1].

$$BMI = \frac{\text{mass}(kg)}{height^2(m^2)} \quad [1]$$

Skinfold thicknes and arm circumference measurements were performed as recommended by the International Standards for Anthropometric Assessment Manual (Olds, Stewart, Carter & Marfell-Jones, 2006). All measurements were performed on the right side of the body. Arm circumference was measured in standing position, with arms relaxed at the side, using standard metric tape measure. The point of measurement was the midpoint between the most superior and lateral part of the acromion border and the most proximal and lateral border of the head of the radius. Measurement was performed at the eye level and to the nearest 1 mm.

Skinfold thickness measures (SFTM) were obtained at m. biceps brachii, m. triceps brachii and subscapular area with skinfold caliper (Harpendem Skinfold Caliper, Baty International, Burgess Hill, UK) according to the manufacturer's instructions and International Standards for Anthropometric Assessment Manual (Olds, Stewart, Carter & Marfell-Jones, 2006). Body fat percentage (BF%) was calculated from arm circumference, SFTM and height of participant according to equation [2] specifically developed and validated on pregnant women by Knnieappan, Deussen, Grivell, Yelland & Dodd (2013). SFTM were measured in mm, while arm circumference and height were measured in cm.

$$BF\% = 12.7 + 0.457\ x\ triceps\ SFTM + 0.352\ x\ subscapular\ SFTM + 0.103\ x\ biceps\ SFTM - 0.057\ x\ height + 0.265\ x\ arm\ circumference \quad [2]$$

Neonatal weight, length, Apgar score and health status data were extracted from the hospital discharge letter and body mass index [1] and neonatal ponderal index (PI) [3] have been calculated according to standard equations.

$$PI = \frac{weight(g)}{length^3(cm^3)} x100 \quad [3]$$

### 6.3.2 Assessment of physical activity

Physical activity of the pregnant women was assessed at baseline and in the 30th and the 36th week of the pregnancy using Pregnancy Physical Activity Questionnaire (PPAQ) (Chasan-Taber et al., 2004). PPAQ is a reliable and valid instrumet which provides reasonable measure of physical activity of pregnant women. It measures type, duration and frequency of physical activities performed by pregnant women. It is self-administered and reports the time spent in 32 activities including household/caregiving activities, occupational activities, sports/exercise, transportation activities and inactivity. We used the recall period of last six weeks. The questionnaire asked the pregnant women to report estimated frequency and duration spent in specific activities (i.e. "none", "less than 1/2 hour per day", "1/2 to 1 hour per day", "1 to 2 hours per day", "2 to 3 hours per day", "3 or more hours per day") during the last 6 weeks. Scoring of the questionnaire was provided by the author of the questionnaire who also granted a written permission to use the PPAQ for this particular trial (Appendix 4). An estimated average metabolic equivalent (MET-hour/week) value was calculated by multiplying the duration of the time spent in each activity and established categorical intensity value associated with the question. Activities were categorized by type and intensity, and values for every category calculated.

### 6.3.3 Blood analyses

The OGTT and blood glucose profiles were performed in the medical biochemistry laboratory at the Referral Centre for Diabetes, University Clinic for Diabetes, Endocrinology and Metabolic Diseases Vuk Vrhovac, University Hospital Merkur in Zagreb, Croatia according to standard operating protocols for the accredited laboratory (International Standards Organization (ISO) 15189 Medical laboratories – particular requirements for quality and competence) and according to recommendations of the Croatian Chamber of Medical Biochemists (Vucic Lovrencic, Honovic, Kralik & Matica, 2012). Laboratory staff were blinded. A seventy-five gram OGTT was performed immediately before, and at 60 and 120 minutes after glucose ingestion. Only venous plasma was used for glucose measurement. The laboratory report of the test contained cut-off values according to IADPSG criteria (Metzger et al., 2010). Results were expressed as mmol/L.

After establishing the diagnosis by OGTT, all pregnant women from the trial were further tested monthly or bi-monthly for their fasting and postprandial glucose levels until the end of pregnancy. Four capillary blood samples were taken, before the first meal in the morning, 2 h after breakfast, 2h after lunch and 2 h after dinner respectively. We took into our final analysis their last blood glucose profile, which was analysed between the 38th and the 40th week of pregnancy. Variables taken into account were fasting blood glucose and average value of postprandial glucose values.

## 6.4 Intervention

Pregnant women in the experimental group were included in an individualized, physiotherapist-led, structured exercise programme two times per week, along with their standard prenatal care. Duration of the exercise session was 50-55 minutes. Furthermore, they were instructed to perform at least 30 minutes of vigorous walking once per day, preferably after meal. Participants from the experimental group started with their exercise sessions after an established diagnosis of GDM and they exercised throughout the whole duration of pregnancy. Attendance was recorded at every exercise session and they were instructed to keep a diary of walks on a daily basis. The minimum duration of the intervention was set at 6 weeks and attendance at 70% of calculated expected exercise sessions between the time of inclusion in the trial and the 38th week of pregnancy. Pregnant women in the control group received only standard prenatal care for women with GDM. They were not discouraged from exercising on their own.

### 6.4.1 Medical nutrition therapy

All participants were put on medical nutrition therapy (MNT) for pregnant women with GDM developed by the Referral Centre for Diabetes, University Clinic for Diabetes, Endocrinology and Metabolic Diseases Vuk Vrhovac, University Hospital Merkur in Zagreb, Croatia (Appendix 5). Their diet included 1800 kcal per day, 20% of proteins (90g), 30% of fat (60 g) and 50% of carbohydrates (225 g) respectively, distributed over three main meals and three snacks.

### 6.4.2 Exercise programme

The exercise programme was developed in accordance with the current guidelines for exercise in pregnancy (ACOG, 2002; RCOG, 2006) and we strictly complied with absolute and relative contraindications for exercise and warning signs for termination of exercise. Jumps, sharp and sudden changes of movement directions and body positions, deep lunges, trunk rotations and supine position were avoided.

Exercise sessions were performed twice per week with duration of 50-55 minutes. In order to achieve good adherence to protocol, the pregnant women could chose the days of the week when they wanted to exercise and were also able to chose the most convenient time of the day. All exercise sessions were held in private physiotherapy practice, the room was air-conditioned to 20-22°C, and humidity was 40-60 %. The pregnant women wore standard sports clothing in which they felt comfortable and sports footwear. They were advised to drink enough water during and after exercise sessions, and to have a meal consisting of complex carbohydrates, fat and proteins two hours before the exercise session to prevent hypoglycaemia.

The exercise programme consisted of aerobic exercise (20 minutes), resistance exercises (20-25 minutes), pelvic floor and stretching exercises, and relaxation at the end of session (10 minutes). The aerobic part of the exercise was performed on treadmill (Axos Runner, Heinz Kettler GmbH, Ense-Parsit, Germany) within aerobic zone (65-75% of maximal heart rate), i.e. target values were 13-14 according to The Borg Rating of Perceived Exertion scale (Borg, 1982). Walking on treadmill at normal pace and gradually adjusting velocity and incline of the treadmill allowed proper warm-up for the first 5 minutes of the exercise session. Pregnant women were free to adjust the velocity and incline of the treadmill to achive targeted intensity.

Resistance exercises included exercises for all major muscle groups at each session with the same target values of the Borg Rating of Perceived Exertion scale. Six different exercises were performed in three sets of 10-15 repetitions in each set. Three standardized resistance exercise protocols were developed and interchanged (Appendix 6). Exercises included the trunk muscles and upper and lower limb muscles. They were carried out using body weight, elastic bands (TheraBand, The

Hygenic Corporation, Akron, OH, USA) and hand held weights of 0.5 and 1 kg (Aerobic Dumbbels, Heinz Kettler GmbH, Ense-Parsit, Germany).

Stretching and pelvic floor exercises were performed at the end of every exercise session. All major muscles were covered by stretching. The duration of every stretching exercise was 10-15 seconds and every stretching position was performed only once as our goal was not to increase flexibility. Over-stretching was consistently avoided due to the fact that pregnant women are more prone to injuries secondary to hormonal changes. A short relaxation was performed as the last part of the session to allow proper cool-down.

### 6.4.3 Measurements during exercise sessions

For the safety of the pregnant women and their fetuses, several measurements were taken before, during and after each exercise session. Maternal heart rate (HR) was monitored continuously (Mio Alpha, Mio Global, Vancouver, BC, Canada). Baseline values of heart rate were taken before the session (after 5 minutes of relaxation) and the average values were recorded separately for the aerobic and the resistance part of every exercise session. Target heart rate (THR) was calculated using Karvonen's formula [4]. Maximum HR was determined using traditional formula 220 – age.

$$THR = ((\max HR - resting\ HR)\ x\ \%Intensity) + resting\ HR \qquad [4]$$

Furthermore, arterial blood pressure values were recorded before the exercise, after the aerobic part of the exercise, after resistance exercises and in the end of the session. Blood pressure was measured by mercury sphygmomanometer (Erkameter 300, ERKA, Kallmeyer Medizintechnik, Bad Tölz, Germany) using the first and fifth Korotkoff sound to identify systolic and diastolic values, respectively.

Tympanic membrane temperature was also measured before the exercise, after aerobic and resistance exercise and in the end of the session with an infrared ear thermometer (ThermoScan 6023, Braun GmbH, Kronberg, Germany) (Purssell, While & Coomber, 2009). Although tympanic membrane temperature is not a perfect method of assessing the core temperature because it underestimates core temperature during strenous exercise, we did not expect any serious overheating

where the relationship betwen rectal and aural temperatures is weakest (Huggins, Glaviano, Negishi, Casa & Hertel, 2012) and other methods of measuring core temperature were unacceptable for use in pregnancy and during each exercise session. Tympanic membrane temperature offers simple and non-invasive temperature measurement, it has good correlation with rectal temperature in pregnant woman (Yeo, Hayashi, Wan & Dubler, 1995) and it has already been used in a similar trial (Larsson & Lindquist, 2005).

Furthermore, the fetal heart rate was periodically monitored during every exercise session. Baseline value was taken before the session (after 5 minutes of relaxation) which was repeated after the aerobic and resistance part of the exercise. Final value was taken at the end of the session. An ultrasound device with doppler effect with the accuracy of ± (2% +1 digit) was used to measure the fetal heart rate (MAS Baby Watcher, MAS Future Medical GmbH, Leibnitz, Austria).

Capillary blood samples were collected on three ocassions for glucose levels testing, and on two occasions for lactate levels testing before and after the resistance part of the exercise session to assess for hypoglycaemia and exercise intensity. Analyses were performed using reliable and valid hand held device (Accutrend Plus, Roche Diagnostics, Basel, Switzerland) and test strips (Accutrend Glucose, Roche Diagnostics, Basel, Switzerland; BM-Lactate, Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. Quality control was regularly performed using control solutions (Accutrend Control G, Roche Diagnostics, Basel, Switzerland; BM-Control Lactate, Roche Diagnostics, Basel, Switzerland). Despite the tendency to overestimate glucose levels, the device showed a good agreement with the laboratory method and good analytical performance for glucose levels testing (Solnica & Naskalski, 2005; Conquiero Rda et al., 2014). Furthermore, Accutrend Plus is also accurate and reliable for lactate levels testing and considered suitable for sports research field (Baldari et al., 2009).

## 6.5 Statistical analyses

Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). Descriptive statistics were performed for all variables of interest and included mean value, standard deviation, as well as minimal and maximal value where

appropriate. The Shapiro-Wilk test was performed to check for normality of data and Levene's test to check for homogeneity of variances. Where the assumptions of normality and homogeneity of variances were met, variables were analysed using the T-test. Non-normal distributed and categorical data were analysed with the Mann-Whitney U test.

Specifically, the Mann Whitney U test was used to compare baseline participants' characteristics and analyse and compare the results of PPAQ, the rate of complications in pregnancy and during labour and delivery, maternal anthropometrical measurements during specific time points of pregnancy, neonatal Apgar scores, the rate of neonatal complications and neonatal anthropometrical data between groups. Two-tailed Mann Whitney U test without Bonferroni correction was used. The paired-samples T-test was used to test for significant differences between baseline values and values at specific time points and periods during the exercise session regarding physiological data (maternal and fetal HR, glucose and lactate levels, tympanic membrane temperature and blood pressure). An independent samples T-test was used to test for significant differences in fasting and postprandial glucose values taken at the end of pregnancy.

The degree of relationship between variables was calculated using Pearson's correlation coefficient ($r$) and the point-biserial correlation coefficient ($r_{pbi}$). Pearson's correlation coefficent ($r$) was used to determine the degree of relationship between continuous variables. Specifically, it was used to calculate the correlation coefficient between main outcomes (fasting and postprandial glucose levels, neonatal anthropometrical data) and body mass and weight gain in specific pregnancy periods, as well as activity levels measured by the PPAQ. Also, maternal anthropometrical measures were correlated with baseline data and levels of physical activity during pregnancy.

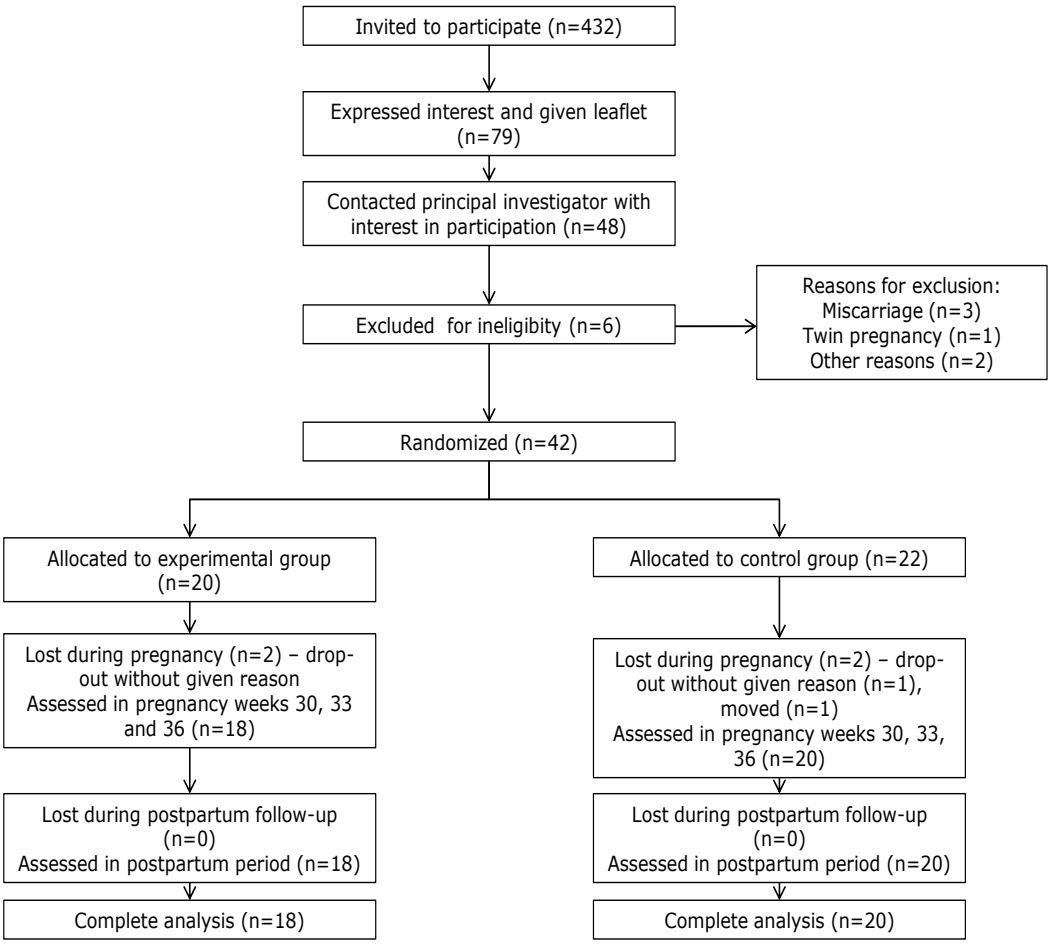
The point-biserial correlation coefficient ($r_{pbi}$) was used to determine the degree of relationship between dichotomous nominal and continuous variables. Specifically, it was used to determine the relationship between main outcomes (fasting and postprandial glucose levels, neonatal anthropometrical data) and baseline characteristics of the sample (family history, parity, pre-pregnancy physical activity etc.), as well as the relationship between complications in pregnancy and during labour and delivery with maternal anthropometrical measures and activity levels measured by the PPAQ.

The level of significance was set at $P < 0.05$, Cohen's d (*d*) and effect size (*r*) were calculated for all outcome variables with the level of significance ≤ 0.05.

# 7 RESULTS

A total of 42 pregnant women diagnosed with GDM were finally enrolled and randomized in the trial from November 2013 till September 2014, 20 in the experimental group and 22 in the control group. All follow-up procedures were completed by November 2014. Four participants (9.52%) dropped out of the trial, two from the experimental group (10%) and two from the control group (9.09%). The final sample for analysis was 38 pregnant women, 18 in the experimental group and 20 in the control group. Figure 2 shows the flow chart of study participants.

*Figure 2: Flow chart of study participants.*



## 7.1 Participants characteristics

We used the Mann-Whitney U test for comparison of baseline participants' characteristics. The experimental and the control group were well matched, without significant statistical differences in baseline variables (Table 2) ($P > 0.05$).

## 7.2 Characteristics of exercise sessions

A total of 365 exercise sessions were performed during the trial, with 20.28 ± 7.68 sessions per subject on average. The minimum number of exercise sessions per subject was 12, and the maximum 34 exercise sessions. We further divided the experimental group into two subgroups: early-intervention and late-intervention, according to whether they started their exercise sessions before the 27th week of pregnancy. Seven pregnant women (38.89%) were included in the early-intervention subgroup. General characteristics of exercise sessions are shown in Table 3. The average adherence to exercise protocol regarding performed versus planned sessions was high (84.22%), above 70% treshold, which made the intervention 100% successful for all participants in the experimental group.

*Table 3: General characteristics of exercise sessions.*

| Variable | Mean ± SD | Minimum | Maximum |
|---|---|---|---|
| Start of the intervention (week of pregnancy) | 25.56 ± 5.20 | 13 | 30 |
| End of the intervention (week of pregnancy) | 37.22 ± 0.81 | 36 | 39 |
| Week of birth | 38.89 ± 0.90 | 38 | 40 |
| Period between last exercise session and birth (weeks) | 1.67 ± 0.84 | 0 | 3 |
| Exact duration of the intervention (weeks) | 12.22 ± 5.08 | 7 | 23 |
| Expected number of exercise sessions | 24.39 ± 10.04 | 14 | 46 |
| Exact number of exercise sessions | 20.28 ± 7.68 | 12 | 34 |
| Percentage of the exact number of exercise sessions versus expected number of sessions (%) | 84.22 ± 8.51 | 70 | 96 |

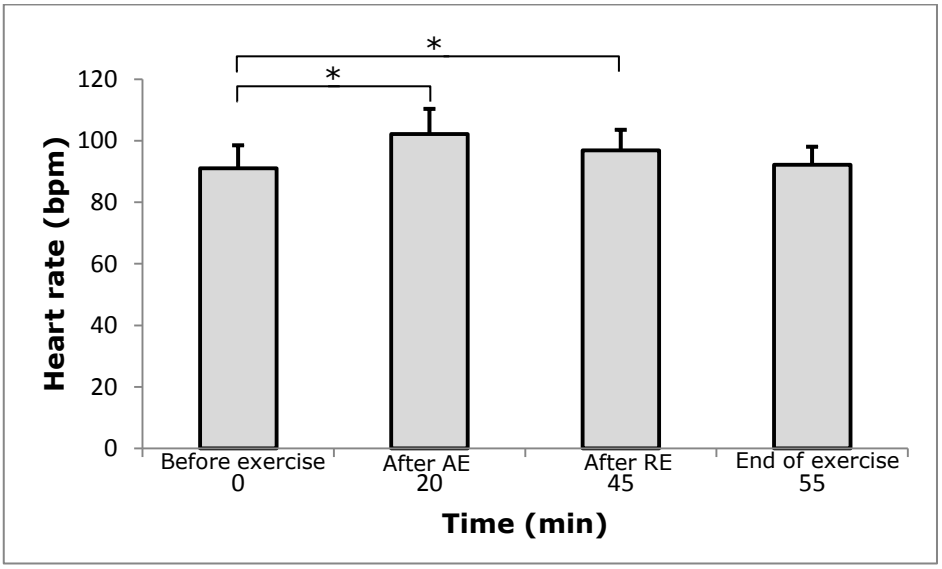
| | | | |
|---|---|---|---|
| Number of missed execrise sessions | 4.11 ± 3.39 | 1 | 12 |

## 7.3 Acute effects of exercise sessions

Regarding acute affects of exercise sessions, we took into account the maternal heart rate before, during and two minutes after the aerobic and resistance part of exercise session. We also took systolic and diastolic blood pressure, fetal heart rate and tympanic temperature measurements before and in the first two minutes after the aerobic and resistance part of the exercise session. We also analysed changes in capillary blood glucose and lactate leves. All changes between baseline levels and the above mentioned time points are shown in absolute numbers and percentages (Table 4). We used the paired-samples T-test to calculate if there was a significant difference between baseline value and the value at a specific time point of the exerise session.

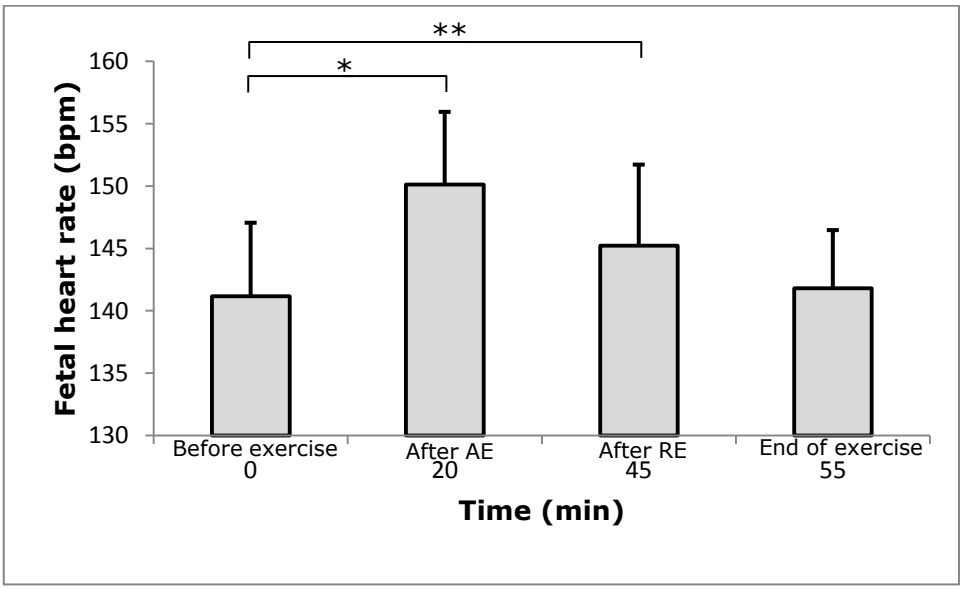
Exercise sessions increased maternal heart rate, fetal heart rate and body temperature ($P < 0.001$) after the aerobic part of the exericise session, as well as maternal heart rate ($P < 0.001$) and fetal heart rate ($P = 0.003$) after resistance exercises (Figures 3-5). However, it is not clear if prevous aerobic exercise could have influenced the maternal and fetal heart rate during the resistance exercise part of the session.

*Figure 3: Average changes in maternal heart rate throughout exercise session.*



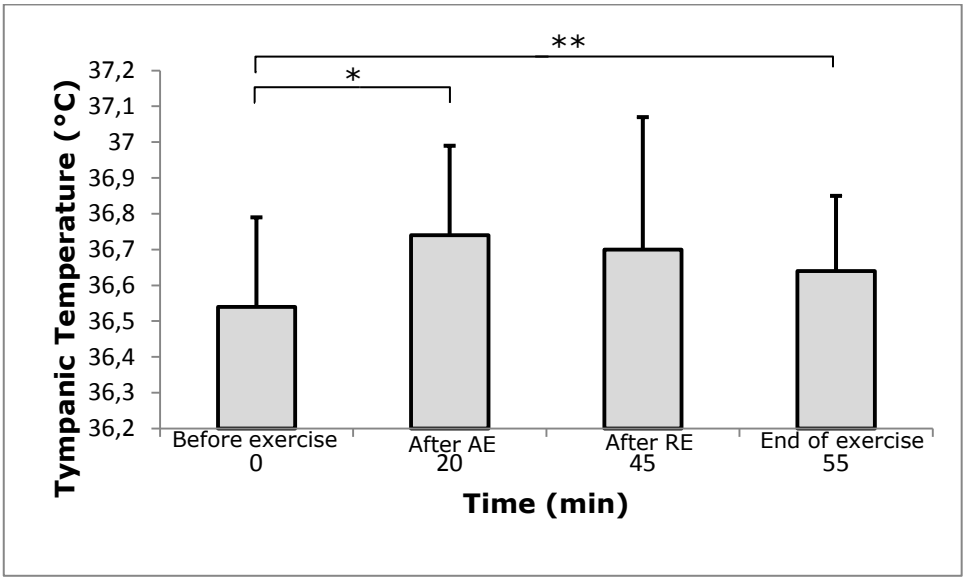

*AE – aerobic exercise; RE – resistance exercise; bpm – beats per minute; * - P* < 0.001.

*Figure 4: Average changes in fetal heart rate throughout exercise session.*




*AE – aerobic exercise; RE – resistance exercise; bpm – beats per minute; * - P < 0.001; ** - P = 0.003.*

*Figure 5: Average changes in body temperature throughout exercise session.*

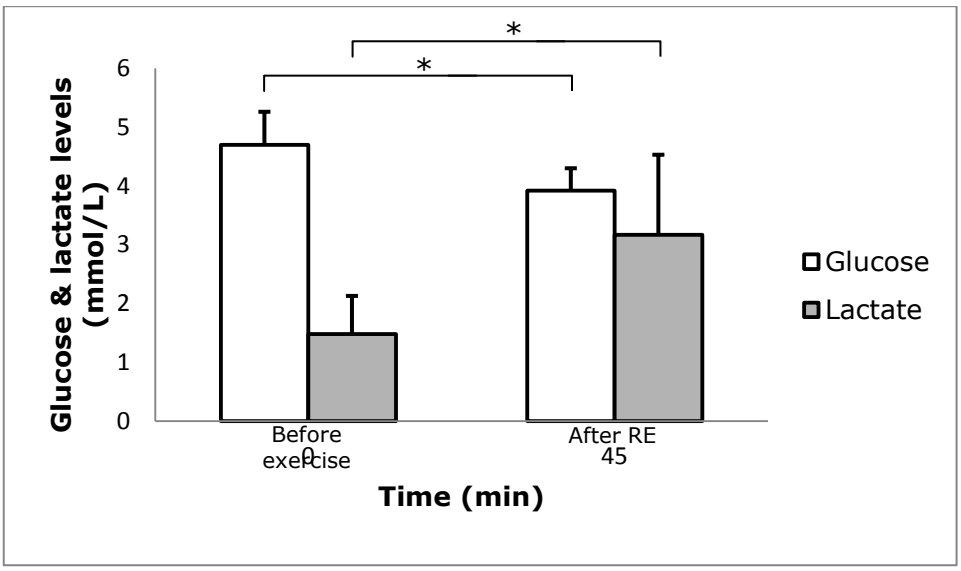



*AE – aerobic exercise; RE – resistance exercise; * - P < 0.001; ** - P* = 0.009.

Furthermore, capillary glucose level significantly dropped from baseline value until the end of the resistance part of the exercise session ($P < 0.001$) (Figure 6), while lactate level increased from the baseline value until the end of the resistance part of the exercise ($P < 0.001$) (Figure 6). Systolic and diastolic pressure did not change during and after the exercise session (Figure 7). All values were set near baseline values at the end of the exercise session.

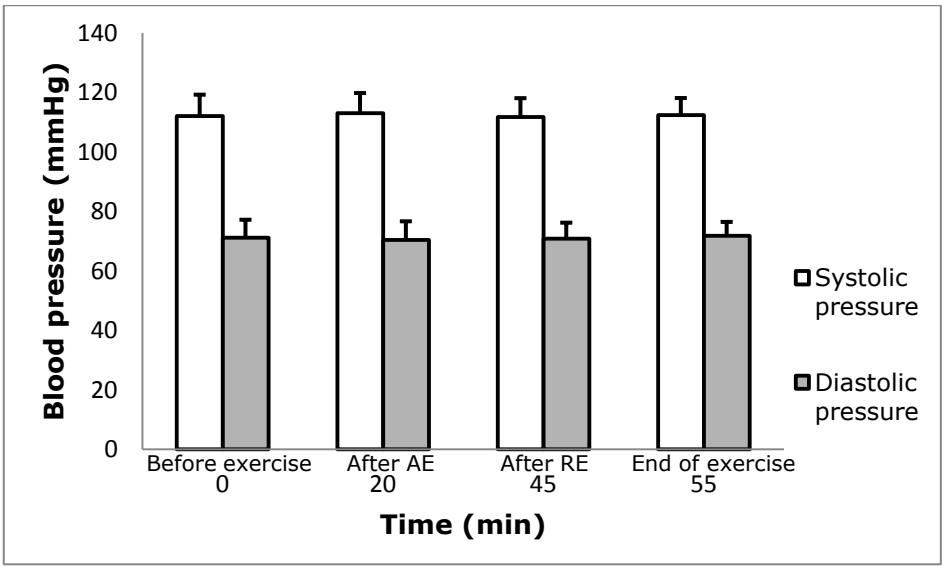
There were no episodes of hypoglycaemia or warning signs which would require terminating exercise during sessions. Also, there were no adverse effects caused by exercise and none of the pregnant women developed relative or absolute contraindications for exercise. We did not detect any overheating, i.e. a dangerous increase in core body temperature.

*Figure 6: Average changes in capillary glucose and lactate levels from the start to the end of resistance part of the exercise session.*




*RE – resistance exercise; * - P < 0.001.*

*Figure 7: Average changes in systolic and diastolic blood pressure throughout exercise session.*




*AE – aerobic exercise; RE – resistance exercise.*

*Table 4: Acute effects of exercise sessions.*

| Variable | Mean ± SD | Min | Max | Average diff. from baseline | % (diff. from baseline) | P (diff. from baseline) |
|---|---|---|---|---|---|---|
| Values before the exercise session | | | | | | |
| HR (bpm) | 91.01 ± 7.52 | 76.24 | 106.64 | | | |
| Systolic blood pressure (mmHg) | 112.09 ± 7.12 | 101.88 | 128.68 | | | |
| Diastolic blood pressure (mmHg) | 71.18 ± 6.00 | 60.87 | 81.36 | | | |
| FHR (bpm) | 141.17 ± 5.90 | 129.27 | 153.00 | | | |
| Tympanic temperature (°C) | 36.54 ± 0.25 | 36.09 | 36.85 | | | |
| Glucose (mmol/L) | 4.70 ± 0.56 | 3.70 | 5.63 | | | |
| Lactate (mmol/L) | 1.48 ± 0.65 | 0.95 | 3.55 | | | |
| Values after the aerobic part of the exercise session | | | | | | |
| HR (bpm) | 102.15 ± 8.21 | 87.00 | 116.87 | 11.14 | 12.24 | < 0.001 |
| Systolic blood pressure (mmHg) | 112.96 ± 6.80 | 101.47 | 129.55 | 0.87 | 0.77 | 0.137 |
| Diastolic blood pressure (mmHg) | 70.37 ± 6.28 | 61.06 | 81.50 | -0.81 | -1.14 | 0.408 |
| FHR (bpm) | 150.12 ± 5.84 | 140.06 | 163.33 | 8.95 | 6.34 | < 0.001 |
| Tympanic temperature (°C) | 36.74 ± 0.25 | 36.28 | 37.13 | 0.20 | 0.55 | < 0.001 |

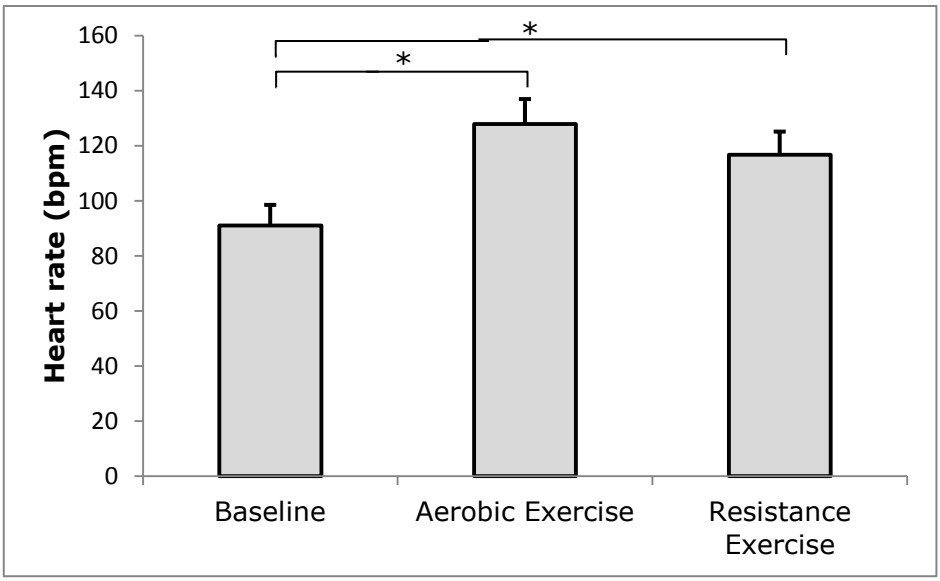
| | | | | | | |
|---|---|---|---|---|---|---|
| Values after resistance exercises | | | | | | |
| HR (bpm) | 96.90 ± 6.67 | 83.44 | 109.73 | 5.89 | 6.47 | < 0.001 |
| Systolic blood pressure (mmHg) | 111.67 ± 6.37 | 99.06 | 124.27 | -0.42 | -0.37 | 0.571 |
| Diastolic blood pressure (mmHg) | 70.84 ± 5.45 | 62.65 | 80.83 | -0.33 | -0.46 | 0.690 |
| FHR (bpm) | 145.23 ± 6.50 | 135.40 | 156.95 | 4.06 | 2.89 | 0.003 |
| Tympanic temperature (°C) | 36.70 ± 0.37 | 35.66 | 37.35 | 0.15 | 0.41 | 0.070 |
| Glucose (mmol/L) | 3.92 ± 0.38 | 3.07 | 4.47 | -0.78 | -16.60 | < 0.001 |
| Lactate (mmol/L) | 3.17 ± 1.36 | 1.25 | 5.45 | 1.69 | 114.19 | < 0.001 |
| Values at the end of the exercise session | | | | | | |
| HR (bpm) | 92.18 ± 5.88 | 82.36 | 101.86 | 1.17 | 1.29 | 0.195 |
| Systolic blood pressure (mmHg) | 112.41 ± 5.67 | 103.00 | 124.00 | 0.32 | 0.29 | 0.603 |
| Diastolic blood pressure (mmHg) | 71.81 ± 4.63 | 64.38 | 78.60 | 0.63 | 0.86 | 0.400 |
| FHR (bpm) | 141.82 ± 4.66 | 134.47 | 150.96 | 0.65 | 0.46 | 0.290 |
| Tympanic temperature (°C) | 36.64 ± 0.21 | 36.31 | 36.93 | 0.10 | 0.27 | 0.009 |

*min – minimum; max – maximum; diff. – difference; HR – heart rate; bpm – beats per minute; FHR – fetal heart rate.*

### 7.3.1 Characteristics and acute effects of aerobic and resistance exercises

Exercise sessions were divided into two main parts: aerobic exercise (AE), which included vigorous walking on treadmill, and resistance exercises (RE). General characteristics and acute effects of AE and RE are shown in Table 5. We achieved satisfactory exercise intensity in both parts of each exercise session, with the average intensity of 65.06 ± 4.42% of maximal heart rate, while maintaining intensity values at 13-14 according to the Borg Rating of Perceived Exertion scale, which was the primary determinant of exercise intensity. Maternal heart rate increased during the aerobic (40.48%; $P < 0.001$) and resistance (28.17%, $P < 0.001$) part of the exercise session in comparison with baseline values (Figure 8).

*Figure 8: Average maternal heart rate during aerobic and resistance parts of exercise session.*




** - P < 0.001.*

*Table 5: Characteristics and acute effects of aerobic and resistance exercises.*

| Variable | Mean ± SD | Min | Max | % (diff. from baseline) | P (diff. from baseline) |
|---|---|---|---|---|---|
| Treadmill velocity (km/h) | 3.88 ± 0.45 | 3.05 | 4.88 | | |
| Treadmill incline (°) | 2.93 ± 1.18 | 0.16 | 4 | | |

| | | | | | |
|---|---|---|---|---|---|
| Average HR during AE (bpm) | 127.85 ± 9.10 | 113.93 | 143.05 | | |
| Max HR (bpm) | 187.39 ± 3.74 | 181 | 196 | | |
| Percentage of max HR during AE (%) | 68.28 ± 5.13 | 60 | 77 | | |
| Difference in HR from baseline during AE | 36.84 ± 8.27 | 25.17 | 61.06 | 40.48 | < 0.001 |
| Average HR during RE (bpm) | 116.65 ± 8.49 | 104.58 | 131.92 | | |
| Percentage of max HR during RE (%) | 62.28 ± 4.98 | 55 | 71 | | |
| Difference in HR from baseline during RE (bpm) | 25.64 ± 7.78 | 15.38 | 43.17 | 28.17 | < 0.001 |
| Average HR during total exercise session (bpm) | 121.87 ± 8.10 | 108.71 | 137.05 | | |
| Percentage of max HR during total exercise session (%) | 65.06 ± 4.42 | 58 | 74 | | |
| Difference in HR from baseline during total exercise session | 30.85 ± 7.47 | 20.61 | 51.91 | 33.90 | < 0.001 |

*min – minimum; max – maximum; diff. – difference; HR – heart rate; AE – aerobic exercise; RE – resistance exercise; bpm – beats per minute.*

## 7.4 Characteristics of performing daily vigorous walking

All pregnant women in the experimental group were asked to vigorously walk every day for at least 30 minutes and keep their walking diaries. This part of the intervention also had a 100% successful adherence to protocol, well above 70%, with the average of 95.56 ± 4.54% regarding planned and performed daily walks (Table 6).

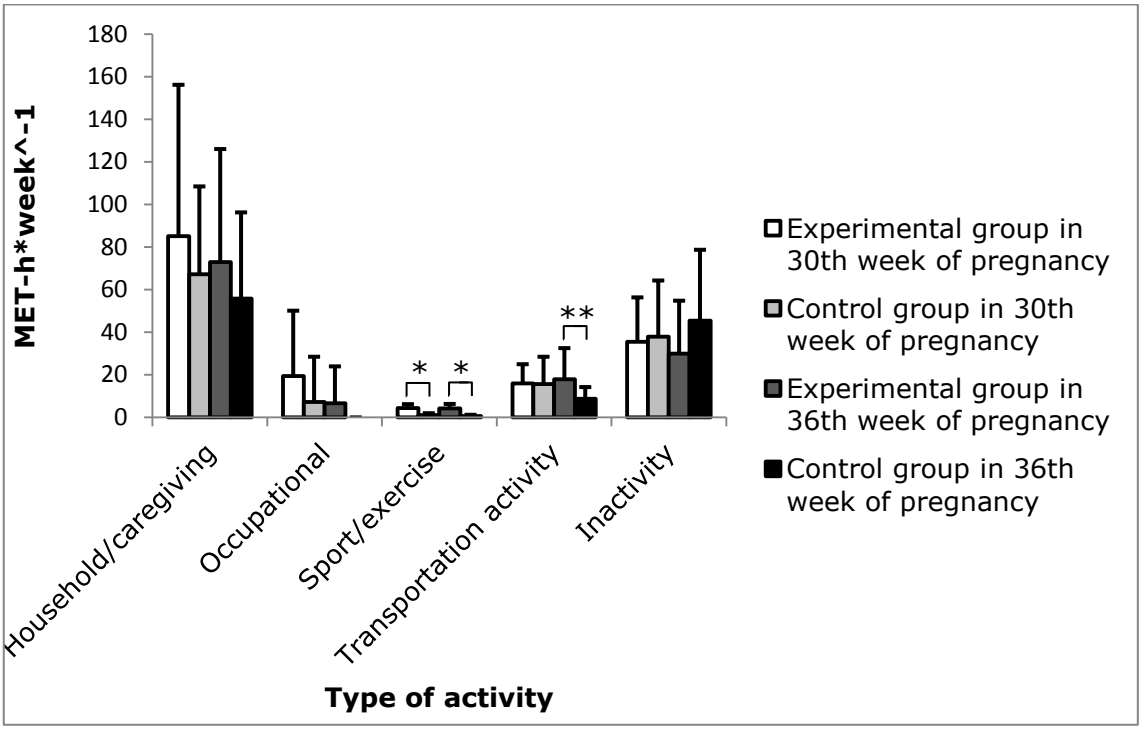
*Table 6: Characteristics of performing daily walks.*

| Variable | Mean ± SD | Minimum | Maximum |
|---|---|---|---|
| Planned vigorous walks | 84.78 ± 33.95 | 49 | 161 |
| Performed vigorous walks | 81.56 ± 34.85 | 43 | 161 |
| Percentage of adherence (%) | 95.56 ± 4.54 | 86 | 100 |

## 7.5 Physical activity in pregnancy questionnaire

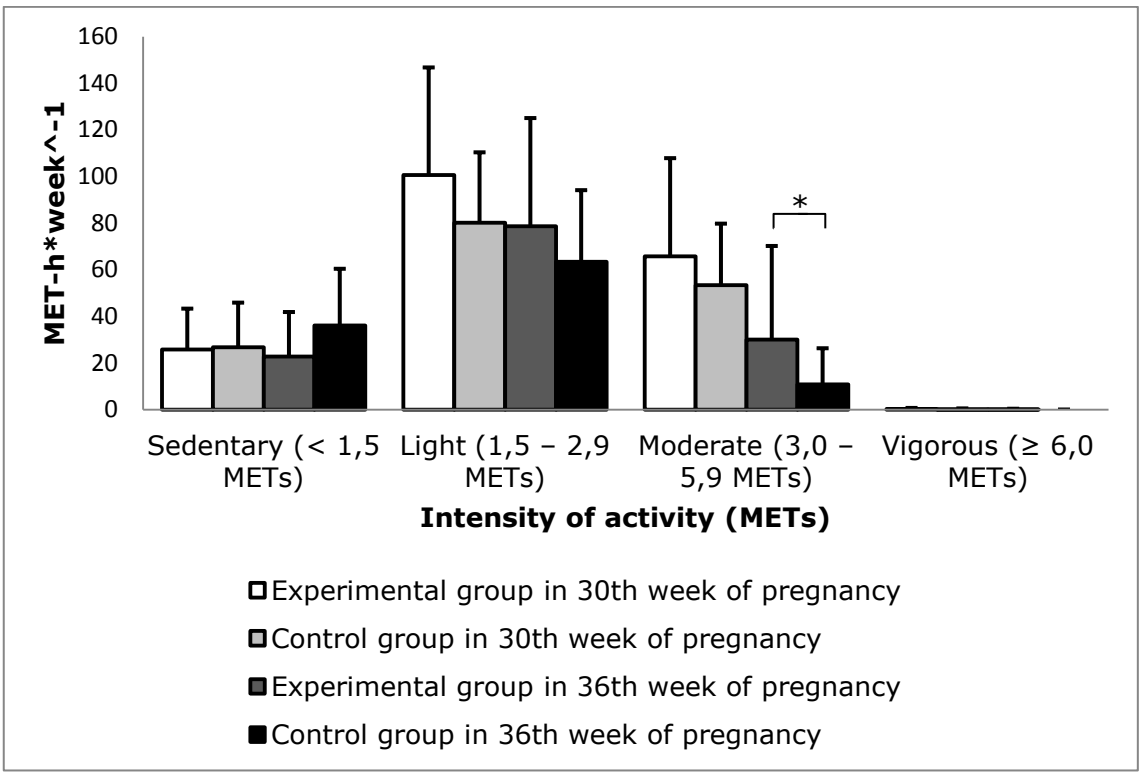
Most of the variables were not normally distributed and the Mann-Whitney U test was used to test for significant differences between the experimental and the control group regarding their total activity, intensity of activity and type of activity (Table 7). While there were no differences in baseline levels of physical activity (Table 2), we found significant differences in the 30th and the 36th week of pregnancy. The most significant difference, with large effect size, was in levels of sport/exercise activities, both during week 30 ($P < 0.001$, $d = 2.37$, $r = 0.76$) and week 36 ($P < 0.001$, $d = 2.41$, $r = 0.77$) when pregnant women in the experimental group had more sport/exercise activities compared to the control group. Also, moderate intensity activities ($P = 0.016$, $d = 0.63$, $r = 0.30$) and transportation activities ($P = 0.024$, $d = 0.82$, $r = 0.38$) were different in the 36th week of pregnancy, in favour of the experimental group. Breakdown of activities by type and intensity in the 30th and the 36th week of pregnancy is shown in Figures 9 & 10. Total activity levels, as well as total activity of light intensity and above is shown in Figure 11.

*Figure 9: Activities by type in 30th and 36th week of pregnancy.*



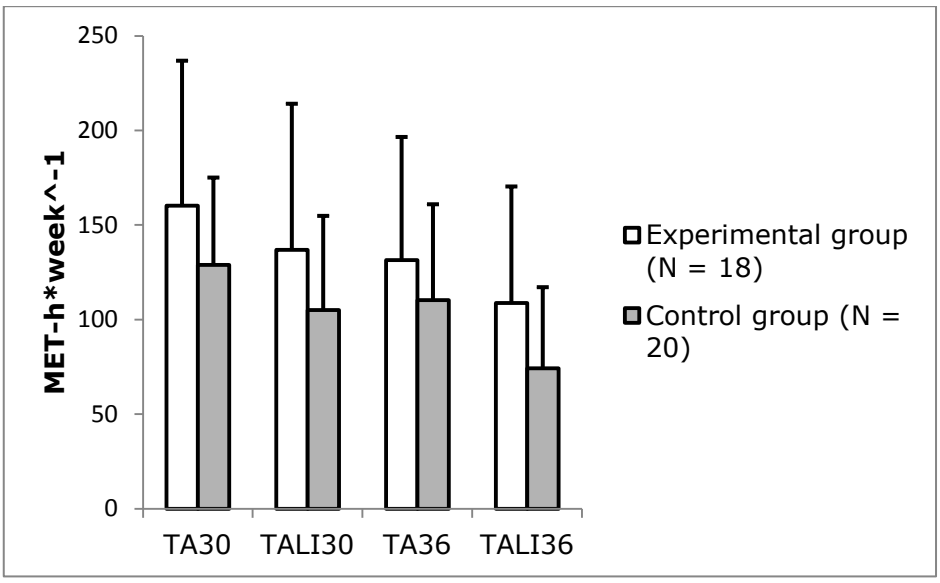

** - P < 0.001; ** - P* = 0.024.

*Figure 10: Activities by intensity in 30th and 36th week of pregnancy.*




*MET – metabolic equivalent; * - P < 0.001.*

*Figure 11: Total activity levels and total activity of light intensity and above in 30th and 36th week of pregnancy.*




*TA30 – total activity in 30th week of pregnancy; TALI30 – total activity of light intensity and above in 30th week of pregnancy; TA36 total activity in 36th week of pregnancy; TALI36 - total activity of light intensity and above in 36th week of pregnancy.*

We detected a general decrease in the amount of activities between the 30th and the 36th week of pregnancy. However, in the experimental group sedentary activities decreased as well, which is opposite to what happened in the control group, where there was an increase in sedentary type of activities, but not statistically significant. Also, participants in the control group reported no vigorous physical activity in the 36th week of pregnancy, opposite to the experimental group, but without significant difference.

Table 7: Results of PPAQ.

| Variable | EG (N = 18; MET-h*week$^{-1}$) Mean ± SD | CG (N = 20; MET-h*week$^{-1}$) Mean ± SD | P |
|---|---|---|---|
| 30th week of pregnancy | | | |
| Total activity | 160.30 ± 76. 54 | 128.85 ± 46.23 | 0.099 |
| Total activity of light intensity and above (≥ 1.5 METs) | 136.87 ± 77.23 | 105.09 ± 49.74 | 0.119 |

| | | | |
|---|---|---|---|
| | By intensity of activity | | |
| Sedentary (< 1.5 METs) | 25.74 ± 17.53 | 26.74 ± 19.10 | 0.965 |
| Light (1.5 – 2.9 METs) | 100.58 ± 46.13 | 80.21 ± 30.09 | 0.196 |
| Moderate (3.0 – 5.9 METs) | 65.70 ± 42.10 | 53.34 ± 26.38 | 0.149 |
| Vigorous (≥ 6.0 METs) | 0.25 ± 0.43 | 0.16 ± 0.32 | 0.654 |
| | By type of activity | | |
| Household/caregiving | 85.06 ± 71.11 | 67.14 ± 41.32 | 0.409 |
| Occupational | 19.41 ± 30.69 | 7.29 ± 21.19 | 0.303 |
| Sport/exercise | 4.43 ± 1.80 | 1.02 ± 0.95 | < 0.001 |
| Transportation activity | 15.99 ± 8.99 | 15.57 ± 12.91 | 0.515 |
| Inactivity | 35.41 ± 20.95 | 37.83 ± 26.45 | 0.988 |
| | 36th week of pregnancy | | |
| Total activity | 131.53 ± 65.00 | 110.35 ± 50.61 | 0.426 |
| Total activity of light intensity and above (≥ 1.5 METs) | 108.75 ± 61.62 | 74.22 ± 42.91 | 0.063 |
| | By intensity of activity | | |
| Sedentary (< 1.5 METs) | 22.78 ± 19.03 | 36.13 ± 24.23 | 0.093 |
| Light (1.5 – 2.9 METs) | 78.63 ± 46.37 | 63.35 ± 30.73 | 0.539 |
| Moderate (3.0 – 5.9 METs) | 30.04 ± 40.10 | 10.87 ± 15.40 | 0.016 |
| Vigorous (≥ 6.0 METs) | 0.09 ± 0.25 | 0.00 ± 0.00 | 0.573 |
| | By type of activity | | |
| Household/caregiving | 72.90 ± 53.11 | 55.70 ± 40.56 | 0.331 |
| Occupational | 6.63 ± 17.33 | 0.00 ± 0.00 | 0.393 |
| Sport/exercise | 4.26 ± 2.07 | 0.55 ± 0.68 | < 0.001 |
| Transportation activity | 17.82 ± 14.71 | 8.76 ± 5.48 | 0.024 |
| Inactivity | 29.93 ± 24.87 | 45.34 ± 33.37 | 0.149 |

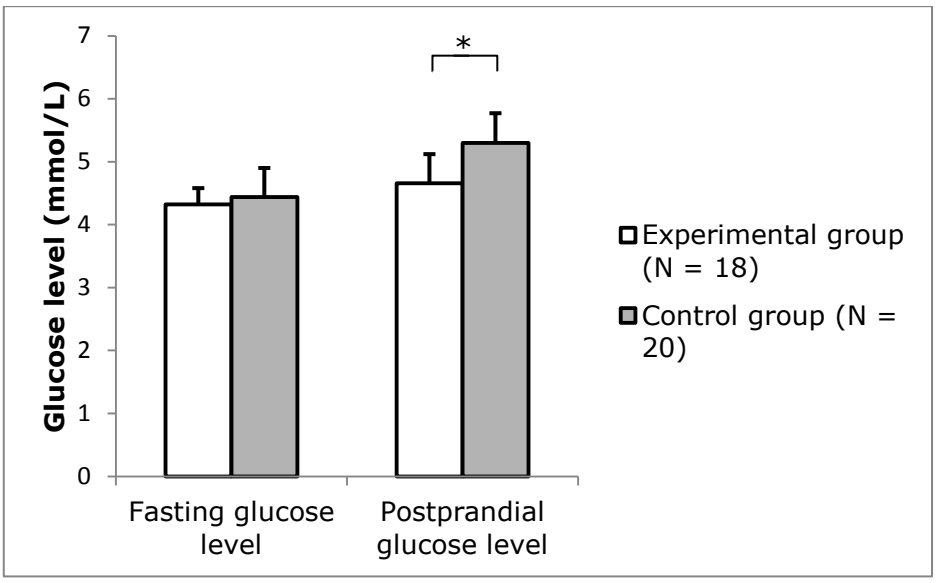
| | | | |
|---|---|---|---|
| Difference between 30th and 36th week of pregnancy (36th – 30th) | | | |
| Total activity | -28.76 ± 58.75 | -18.50 ± 47.64 | 0.851 |
| Total activity of light intensity and above (≥ 1.5 METs) | -28.12 ± 53.33 | -30.00 ± 43.31 | 0.426 |
| By intensity of activity | | | |
| Sedentary (< 1.5 METs) | -2.96 ± 17.58 | 9.39 ± 20.42 | 0.087 |
| Light (1.5 – 2.9 METs) | -21.95 ± 50.70 | -16.86 ± 34.00 | 0.988 |
| Moderate (3.0 – 5.9 METs) | -35.63 ± 15.78 | -42.47 ± 17.37 | 0.593 |
| Vigorous (≥ 6.0 METs) | -0.16 ± 0.47 | -0.16 ± 0.32 | 0.965 |
| By type of activity | | | |
| Household/caregiving | -12.16 ± 36.09 | -11.43 ± 29.64 | 0.942 |
| Occupational | -12.79 ± 30.15 | -7.29 ± 21.19 | 0.806 |
| Sport/exercise | -0.17 ± 2.14 | -0.48 ± 0.94 | 0.919 |
| Transportation activity | 1.83 ± 15.01 | -6.81 ± 10.87 | 0.051 |
| Inactivity | -5.48 ± 26.19 | 7.51 ± 24.16 | 0.133 |

*EG – experimental group; CG – control group; N – sample size; MET – metabolic equivalent.*

## 7.6 Glycaemic control parameters

None of the participants from either group, needed any pharmacological treatment (insulin and/or oral hypoglycaemics). Fasting and postprandial glucose values, taken between the 38th and the 40th week of pregnancy, were analysed by the independent samples T-test (Table 8). While average fasting glucose level was lower in the experimental group, this was not statistically significant (P = 0.367) (Figure 12). On the other hand, the average of 3 postprandial measurements of glucose levels was lower in the experimental group, with large effect size ($P < 0.001$, $d = 1.38$, $r = 0.57$) (Figure 12).

*Figure 12: Average fasting and postprandial glucose levels between 38th and 40th week of pregnancy.*




** - P < 0.001.*

A moderate positive correlation for family history for diabetes ($r_{pbi}$ = 0.342, P = 0.036) and parity ($r_{pbi}$ = 0.398, P = 0.013) was found for fasting glucose level. Also, it was positively correlated with body weight in the 30th and the 36th week of pregnancy, respectively ($r$ = 0.326, P = 0.46; $r$ = 0.343, P = 0.035). On the other hand, pre-pregnancy regular physical activity was negatively correlated with fasting glucose level ($r_{pbi}$ = -0.429, P = 0.007).

Also, a positive moderate correlation for weight gain between the 30th week of pregnancy and labour ($r$ = 0.344, P = 0.034) was found for postprandial glucose levels. There was a strong negative correlation between sport and exercise levels in the 30th and the 36th weeks of pregnancy, respectively, ($r$ = -0.527, P = 0.001; r = -0.537, P = 0.001) and a positive correlation between inactivity levels and postprandial glucose levels ($r$ = 0.369, P = 0.023). We did not find any significant correlations between glycaemic parameters and duration of intervention, adherence to protocol or the number of exercise sessions.

*Table 8: Glucose levels at the end of the pregnancy.*

| Variable | EG (N = 18) | | | CG (N = 20) | | | P |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | Min | Max | Mean ± SD | Min | Max | |
| Fasting glucose level (mmol/L) | 4.32 ± 0.26 | 3.90 | 4.70 | 4.44 ± 0.46 | 3.60 | 5.30 | 0.367 |
| Average of 3 postprandial glucose level (mmol/L) | 4.66 ± 0.46 | 3.67 | 5.60 | 5.30 ± 0.47 | 4.80 | 6.30 | < 0.001 |

*EG – experimental group; CG – control group; N – sample size; min – minimum; max – maximum.*

## 7.7 Complications in pregnancy

Complications in pregnancy were rare, and none of them happened in the experimental group (Table 9). They were analysed by the Mann-Whitney U test. There were no significant differences between groups. Occurence of pregnancy induced hypertension was positively correlated with postprandial glucose levels ($r_{pbi}$ = 0.345, P < 0.001). There was a negative correlation between hypertension and total activity levels in the 36th week of pregnancy ($r_{pbi}$ = -0.328, P = 0.044).

*Table 9: Complications in pregnancy.*

| Variable | EG (N = 18) | CG (N = 20) | P |
|---|---|---|---|
| Pregnancy-induced hypertension (N (%)) | 0 (0) | 2 (10) | 0.806 |
| Preeclampsia (N (%)) | 0 (0) | 1 (5) | 1.000 |
| Other complications (N (%)) | 0 (0) | 0 (0) | 1.000 |

*EG – experimental group; CG – control group; N – sample size.*

## 7.8 Weight gain and fat percentage gain

Differences between groups regarding weight gain and body fat gain were analysed by the Mann-Whitney U test because most of the data were not normally distributed. Also, there were no significant correlations between weight gain and body fat gain and duration of intervention, adherence to protocol or number of exercise sessions. There were some slight differences between groups regarding body weight (Figure 13), body fat percentage and weight gain (Figure 14) during specific time points of pregnancy, but none of them were significant (Table 10).

*Figure 13: Average body mass at specific time points of pregnancy.*

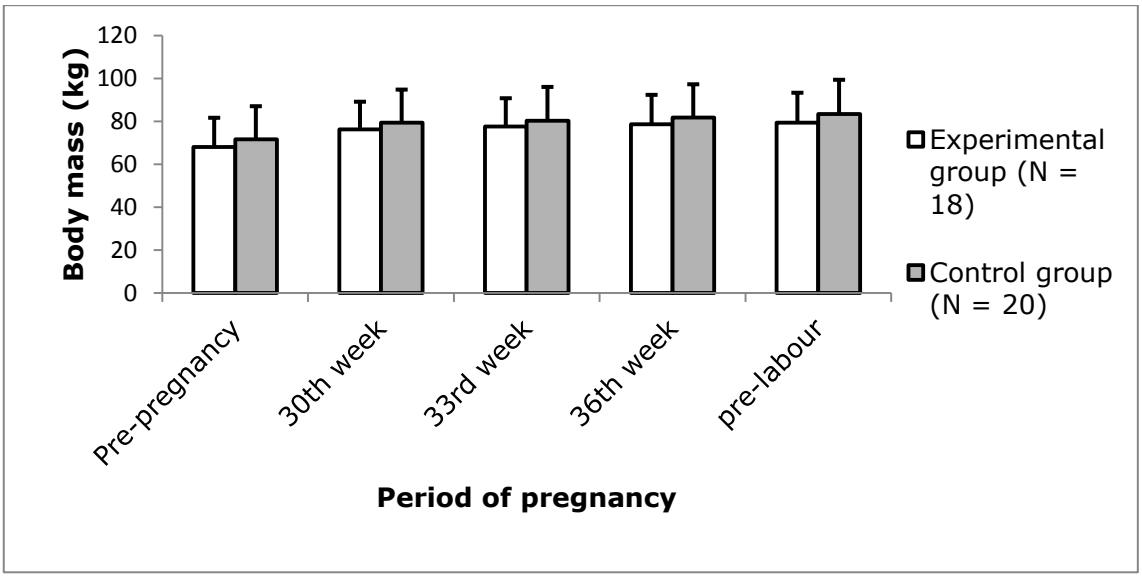


*Figure 14: Average weight gain at specific time periods of pregnancy.*

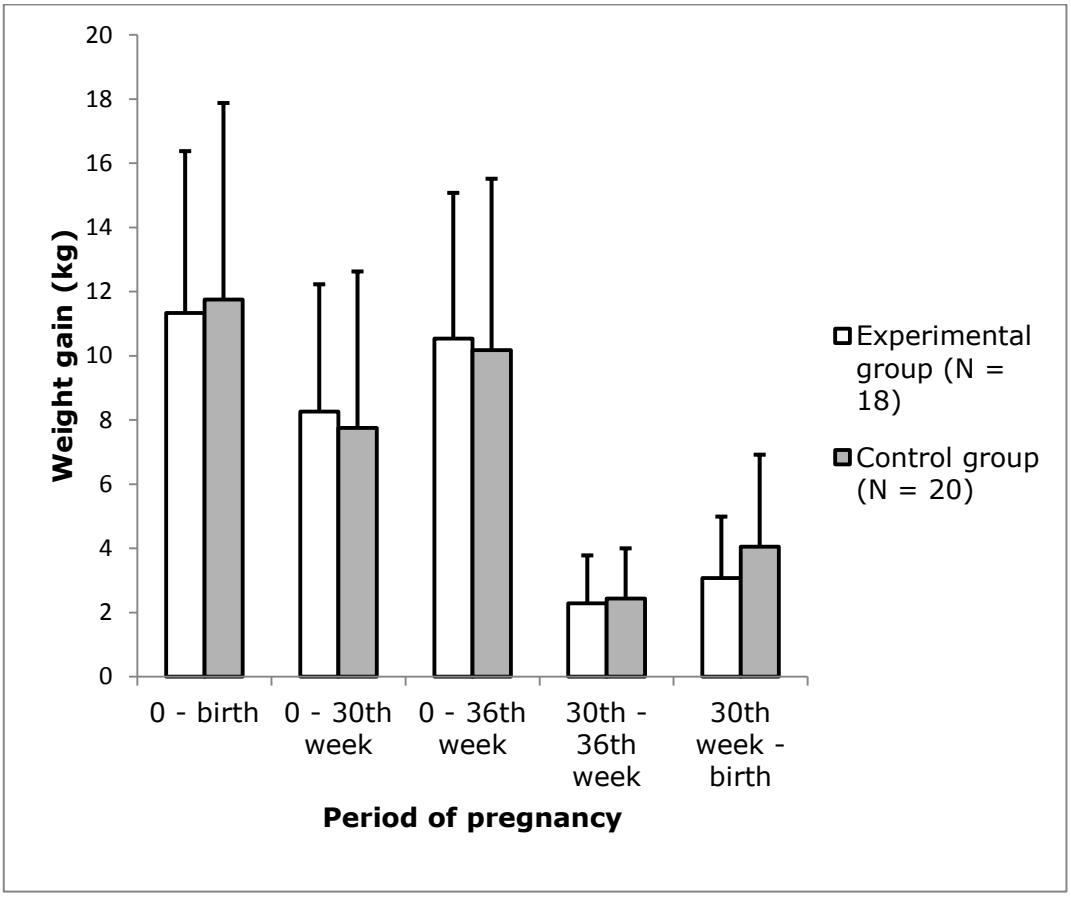



*Table 10: Body weight, weight gan and fat mass gain.*

| Variable | EG (N = 18) Mean ± SD | CG (N = 20) Mean ± SD | P |
|---|---|---|---|
| Pre-pregnancy body mass (kg) | 68.03 ± 13.65 | 71.60 ± 15.48 | 0.515 |
| Pre-pregnancy BMI (kg/m$^2$) | 24.39 ± 4.89 | 25.29 ± 4.65 | 0.515 |
| Body mass in 30th week of pregnancy (kg) | 76.28 ±12.89 | 79.35 ± 15.48 | 0.613 |
| BMI in 30th week of pregnancy (kg/m$^2$) | 27.37 ± 4.70 | 28.03 ± 4.54 | 0.496 |
| Body mass in 33rd week of pregnancy (kg) | 77.57 ± 13.23 | 80.23 ±15.84 | 0.593 |
| BMI in 33rd week of pregnancy (kg/m$^2$) | 27.83 ± 4.80 | 28.34 ± 4.66 | 0.696 |
| Body mass in 36th week of pregnancy (kg) | 78.57 ± 13.80 | 81.78 ± 15.52 | 0.460 |
| BMI in 36th week of pregnancy (kg/m$^2$) | 28.18 ± 5.00 | 28.89 ± 4.55 | 0.478 |
| Body mass before labour (kg) | 79.36 ± 14.00 | 83.35 ± 16.05 | 0.443 |
| BMI before labour (kg/m$^2$) | 28.47 ± 5.11 | 29.44 ± 4.66 | 0.409 |

| | | | |
|---|---|---|---|
| Weight gain from pre-pregnancy till birth (kg) | 11.33 ± 5.05 | 11.75 ± 6.13 | 0.942 |
| Weight gain from pre-pregnancy till 30th week (kg) | 8.26 ± 3.97 | 7.75 ± 4.88 | 0.303 |
| Weight gain from pre-pregnancy till 36th week (kg) | 10.54 ± 4.54 | 10.18 ± 5.34 | 0.478 |
| Weight gain from 30th till 36th week (kg) | 2.28 ± 1.50 | 2.43 ± 1.57 | 0.851 |
| Weight gain from 30th week till birth (kg) | 3.07 ± 1.92 | 4.05 ± 2.87 | 0.331 |
| Arm circumference at 30 weeks (cm) | 28.67 ± 3.69 | 28.89 ± 3.44 | 0.806 |
| M. biceps brachii skinfold at 30 weeks (mm) | 11.58 ± 6.91 | 12.93 ± 5.25 | 0.290 |
| M. triceps brachii skinfold at 30 weeks (mm) | 18.44 ± 6.78 | 18.58 ± 6.77 | 0.784 |
| Subscapular skinfold at 30 weeks (mm) | 21.83 ± 11.01 | 22.35 ± 8.57 | 0.696 |
| Body fat at 30 weeks (%) | 28.08 ±8.02 | 28.68 ± 7.03 | 0.633 |
| Arm circumference at 33 weeks (cm) | 29.40 ± 3.79 | 29.35 ± 3.42 | 0.965 |
| M. biceps brachii skinfold at 33 weeks (mm) | 11.89 ± 7.13 | 14.10 ± 6.09 | 0.158 |
| M. triceps brachii skinfold at 33 weeks (mm) | 19.08 ± 7.54 | 19.15 ± 6.92 | 0.740 |
| Subscapular skinfold at 33 weeks (mm) | 23.56 ± 12.35 | 23.80 ± 9.11 | 0.696 |
| Body fat at 33 weeks (%) | 29.32 ± 9.21 | 29.88 ± 7.48 | 0.675 |
| Arm circumference at 36 weeks (cm) | 28.96 ± 4.04 | 29.74 ± 3.19 | 0.331 |
| M. biceps brachii skinfold at 36 weeks (mm) | 11.50 ± 6.65 | 13.45 ± 4.73 | 0.126 |
| M. triceps brachii skinfold at 36 weeks (mm) | 18.69 ± 6.88 | 19.85 ± 7.60 | 0.633 |
| Subscapular skinfold at 36 weeks (mm) | 23.36 ± 11.60 | 24.40 ± 9.39 | 0.633 |
| Body fat at 36 weeks (%) | 28.80 ± 8.39 | 30.48 ± 7.98 | 0.534 |
| Body fat gain from 30th week till 36th week (%) | 0.72 ± 4.28 | 1.80 ± 2.32 | 0.196 |

*EG – experimental group; CG – control group; N – sample size; BMI – body mass index.*

Arm circumference at the 30th week of pregnancy positively correlated with parity ($r_{pbi}$ = 0.400, P = 0.013) and OGTT 1h result ($r$ = 0.408, P = 0.011). Sports and exercise activities were negatively correlated with m. biceps brachii skinfold in the 36th week of pregnancy ($r$ = -0.349, P = 0.032).

## 7.9 Complications during labour and delivery

Differences between groups regarding the timing of labour, i.e. the gestational week when labour started, were analysed by the Mann-Whitney U test. While the experimental group a had slightly earlier onset of labour, there were no significant differences between groups in birth timing and all subjects gave birth between the 38th and the 40th week of pregnancy (Table 11), with no premature labours.

*Table 11: Gestational week of labour.*

| Variable | EG (N = 18) | | | CG (N = 20) | | | P |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | Min | Max | Mean ± SD | Min | Max | |
| Week of birth | 38.89 ± 0.90 | 38 | 40 | 39.45 ± 0.60 | 38 | 40 | 0.063 |

*EG – experimental group; CG – control group; N – sample size; min – minimum; max – maximum.*

Complications during labour and delivery were also analysed by the Mann-Whitney U test because the data were not normally distributed. There were more labour inductions in the control group, but without significant difference. Also, there was no substantial difference in rates of prolonged labour, instrumental delivery and Caesarean section (Table 12).

A positive correlation between age and Caesarean section was detected ($r_{pbi}$ = 0.370, P = 0.022). Also, m. biceps brachii skinfold in the 30th and the 36th week of pregnancy and body fat percent in the 30th week of pregnancy positively correlated with Caesarean delivery ($r_{pbi}$ = 0.570, P < 0.001; $r_{pbi}$ = 0.441, P = 0.006; $r$ = 0.347, P = 0.033), which also positively correlated with BMI in the 30th and the 36th week of pregnancy, respectively ($r_{pbi}$ = 0.408, P = 0.011; $r_{pbi}$ = 0.402, P = 0.012).

Prolonged labour was positively correlated with weight gain from the 30th week of pregnancy unitl labour ($r_{pbi}$ = 0.372, P = 0.021).

*Table 12: Complications during labour and delivery.*

| Variable | EG (N = 18) | CG (N = 20) | P |
|---|---|---|---|
| Prolonged labour (N (%)) | 1 (5.56) | 2 (10) | 0.633 |
| Labour Induction (N (%)) | 3 (11.11) | 7 (35%) | 0.346 |
| Instrumental delivery (N (%)) | 1 (5.56) | 0 (0) | 0.784 |
| Caesarean section (N (%)) | 5 (27.78) | 5 (25) | 0.696 |

*EG – experimental group; CG – control group; N – sample size.*

## 7.10 Neonatal parameters

The Mann-Whitney U test was used to analyse neonatal data because of the non normal distribution. There were no unfortunate outcomes and serious neonatal complications following birth. Also, no macrosomia or neonatal hypoglycaemia were reported. Apgar scores were without significant differences, as well as the rate of neonatal complications (Table 13).

*Table 13: Neonatal complications.*

| Variable | EG (N = 18) | CG (N = 20) | P |
|---|---|---|---|
| Apgar 1 minute (mean ± SD) | 9.89 ± 0.47 | 9.80 ± 0.70 | 0.828 |
| Apgar 5 minutes (mean ± SD) | 10 ± 0.00 | 10 ± 0.00 | 1.000 |
| Neonatal hypoglycaemia (N(%)) | 0 (0) | 0 (0) | 1.000 |
| Other neonatal complications (N(%)) (hyperbilirubinaemia) | 0 (0) | 1 (5) | 0.806 |

*EG – experimental group; CG – control group; N – sample size.*

Neonatal weight (Figure 15), length and PI were without significant differences between groups (Table 14). However, there was a significant difference in neonatal BMI, which was a little higher in the experimental group, but with moderate effect size (P = 0.035, $d$ = -0.76, $r$ = -0.35) (Figure 16). Newborns' BMI was positively correlated with the week of establishing maternal diagnosis of GDM ($r$ = 0.340, P =

0.037). Percentage of exercise intensity was negatively correlated with neonatal body weight ($r$ = -0.481, P = 0.043) and BMI ($r$ = -0.469, P = 0.05).

*Table 14: Neonatal parameters.*

| Variable | EG (N = 18) Mean ± SD | CG (N = 20) Mean ± SD | P |
|---|---|---|---|
| Neonatal body mass (g) | 3514.45 ± 413.57 | 3377.00 ± 494.27 | 0.393 |
| Neonatal length (cm) | 50.11 ± 2.25 | 50.25 ± 2.51 | 0.851 |
| Neonatal PI (kg/m$^3$) | 2.66 ± 0.63 | 2.65 ± 0.16 | 0.093 |
| Neonatal BMI (kg/m$^2$) | 13.96 ± 0.97 | 13.21 ± 1.01 | 0.035 |

*EG – experimental group; CG – control group; N – sample size; PI – ponderal index; BMI – body mass index.*

*Figure 15: Neonatal body mass.*

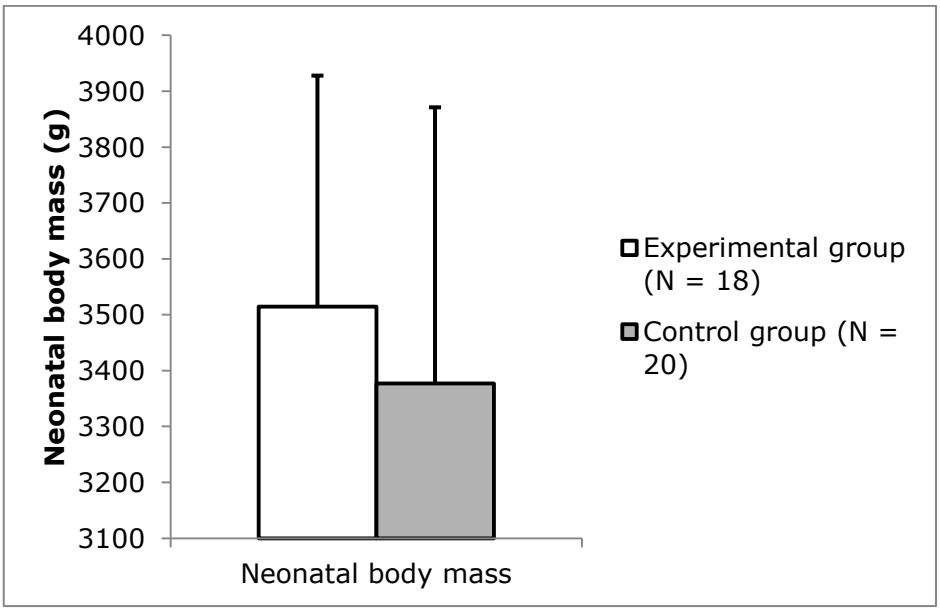
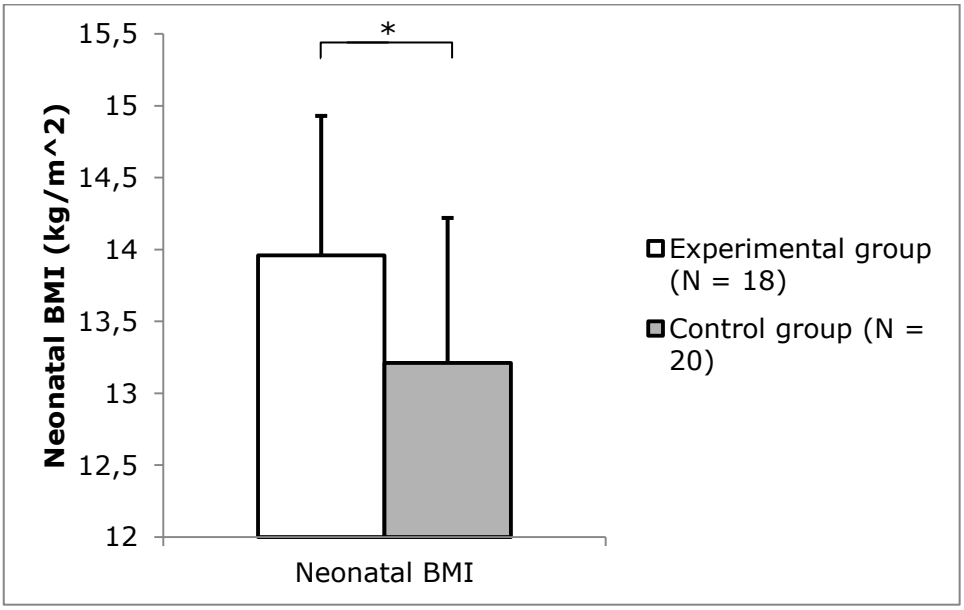


*Figure 16: Neonatal body mass index.*




** - P < 0.001.*

# 8 DISCUSSION

In the present thesis, the aim was to investigate the impact of structured aerobic and resistance exercise on the course and outcome of gestational diabetes mellitus. The thesis covers three main areas. Firstly, it investigates the impact of the proposed exercise programme on maternal health during pregnancy, along with delivery outcomes. Secondly, it explores the influence of the exercise on neonatal health parameters. Finally, it covers maternal weight gain during pregnancy, including body fat percentage changes. In addition, we wanted to explore the acute effects of the exercise programme on several physiological parameters to assess overall safety of exercising at this intensity, duration and frequency.

The motivation for this study was a significant increase in obesity and sedentary lifestyle related diseases, especially diabetes mellitus, worldwide. Also, intrauterine environment and metabolic disorders affects the fetus and have long-lasting effects on future generations (El Hajj et al., 2014). Furthermore, there is still not enough evidence on the effects of exercise in pregnancy for pathological conditions such as GDM. Physical activity and exercise have many positive effects, but we wanted to add more valuable evidence for specific use of exercise in GDM population.

To the best of our knowledge, this is the first study to evaluate the combination of aerobic and resistance exercise among GDM patients. Also, this is the second study to investigate individual exercise programme effects on GDM population, and the first to investigate an individual exercise programme of this type. Furthermore, data from this study represents the most comprehensive information up to date regarding the acute effects of exercise among GDM population.

Physical activity became the cornerstone of health promotion and disease prevention, not only for non-pregnant population, but also for pregnant women. All major guidelines on antenatal healthcare (ACOG, 2002; Davies et al., 2003, RCOG, 2006) recommend exercise in pregnancy for pregnant women without contraindications. Furthermore, American Diabetes Association (2015) and ACOG (2001) recommend exercising for GDM population.

The percentage of pregnant population with GDM diagnosis who exercise regularly according to official guidelines is still not known, but overall, it is still too low,

between 4.3 and 48.8%, depending on the population, and should be improved (Evenson et al., 2004; Walsh et al., 2011; Liu et al., 2011; Domingues & Barros, 2007). There are no data for pregnant Croatian population, but we presume that these numbers are similar to the European population since the study performed by Jurakic et al. (2009) found that physical activity levels in Croatian population in general do not differ considerably from the average amount of physical activity in the European Union countries.

## 8.1 Acute effects of exercise

During the exercise sessions there were no warning signs which would require termination of exercise. Also, there were no adverse effects caused by exercise. None of the pregnant women from the experimental group developed relative or absolute contraindications for exercise. The experimental exercise protocol proved to be completely safe for the pregnant women involved in the trial.

The average adherence to the exercise protocol was very high, 84.22%. We believe this is because all exercise sessions were individual and women could choose the time and day of the week when they were able to attend exercise sessions. The intervention was tailored to their individual needs and capabilities, and also family and/or work obligations. Also, all exercise sessions were guided by the same person, a physiotherapist, who maintained an excellent professional relationship. An individual approach eliminated many reported barriers to exercise in pregnancy.

Also, women were motivated by other factors, too. They were able to see acute changes in blood glucose levels before and after the exercise and they were able to hear the fetal heart rate on every exercise session, which provided some re-assurance to them. This all led to excellent adherence to protocol and we were able to keep them in active exercise regime until very late in the pregnancy (on average until 37.22 ± 0.81 gestational week). The average period between the last exercise session and childbirth was 1.67 ± 0.84 week.

Exercise sessions resulted in significant physiological changes regarding the average heart rate, fetal heart rate, tympanic temperature, capillary blood glucose and lactate levels. Systolic and diastolic pressure values did not change during the

exercise session. However, heart rate, fetal heart rate and body temperature ($P < 0.001$) after the aerobic part of the exericise session, as well as heart rate ($P < 0.001$) and fetal heart rate ($P = 0.003$) after resistance exercises changed. We did not detect any overheating and the maximal measured tympanic temperature was 37.35°C, after the aerobic part of the session.

The average heart rate before the exercise was 91.01 ± 7.52 bpm, which was increased two minutes after the aerobic part of the session by 12.24% from the baseline. Two minutes after resistance exercises, it was only 6.47% increased in comparison with the baseline level. The average intensity during both parts of the exercise session, aerobic and resistance, was 65.06 ± 4.42% of maximal heart rate, specifically 121.87 ± 8.10 bpm, while maintaining intensity values of 13-14 according to the Borg Rating of Perceived Exertion scale. During the aerobic part of the session, maternal heart rate was increased by 40.48% from the baseline value ($P < 0.001$), with the average heart rate of 127.85 ± 9.10 bpm with the intensity of 68.28 ± 5.13% of calculated maximal heart rate. During the resistance part of the session, maternal rate was increased by 28.17% from the baseline value ($P < 0.001$), with the average heart rate of 116.65 ± 8.49 bpm with intensity of 62.28 ± 4.98 of maximal heart rate. Exercise intensity did not exceed the target zones recommended by Artal & O'Toole (2003).

The average fetal heart rate before the exercise was 141.17 ± 5.90 bpm, which increased to 150.12 ± 5.84 bpm after the aerobic part, by 6.34% or 8.95 bpm. Maximal recorded value of the fetal heart rate after aerobic exercise was 163 bpm. The average fetal heart rate after the resistance part of the exercise was 145.23 ± 6.50 bpm, which is an increase from the baseline by 2.89% or 4.06 bpm. We did not record any decrease in the fetal heart rate below baseline levels. These results are similar to the results from a previous study (Avery et al., 1997), where there was an increase in the fetal heart rate for ten beats per minute over the pre-exercise baseline for approximately 10 minutes in 40% of sessions.

Capillary glucose level dropped ($P < 0.001$) from the baseline value which was 4.70 ± 0.56 mmol/L to 3.92 ± 0.38 mmol/L on average, i.e. it was lowered by 16.6%. This is in accordance with the previous findings that muscular uptake of blood glucose during moderate exercise exceeds hepatic glucose production, which results in a decline in blood glucose level during the activity (Minuk et al., 1981). This result is also similar to a previous trial performed by Halse et al., (2015) where

mean capillary concentrations decreased from 6.3 ± 0.8 mmol/L pre-exercise to 4.9 ± 0.7 mmol/L post-exercise ($P < 0.001$). Davenport et al., (2008) performed the trial on GDM population which was already using insulin therapy. They also had a significant drop in capillary glucose concentrations following the exercise, i.e. walking, from 7.6 ± 0.8 mmol/L to 5.1 ± 1.4 mmol/L at the beginning of the walking programme and 7.0 ± 1.4 mmol/L to 5.1 ± 1.0 mmol/L at the end of the programme ($P < 0.05$).

There were no symptomes of hypoglycaemia and the lowest glucose level measured post-exercise was 3.07 mmol/L, similar to the results of Halse et al., (2015) where it was 3.3 mmol/L. However, as a precaution, pregnant women were advised to have a meal if values after the exercise were below 3.9 mmol/L.

Lactate levels increased ($P < 0.001$) from 1.48 ± 0.65 mmol/L on average to 3.17 ± 1.36 mmol/L, which is an increase of 114.2%. The second part of the intervention, daily walks, was also very successful, with the percentage of adherence of 95.56 ± 4.54%, without any adverse effects.

## 8.2 Impact of exercise programme on glycaemic control

We were able to confirm our hypothesis regarding the parameters of gycaemic control, but only partially. Fasting glucose levels at the end of pregnancy, taken between the 38th and the 40th week of pregnancy were lower in the experimental group, but there was no significant difference ($P = 0.367$). This result was similar to results achieved by Callaway et al., (2010). They performed the trial on obese pregnant population without GDM diagnosis at the time of inclusion and studied the impact of exercise on glycaemic control parameters from the 12th week of pregnancy until delivery. Among other values, they measured fasting glucose levels in the 12th, 20th, 28th and the 36th week of pregnancy. Fasting glucose was lower only in the 28th week of pregnancy in the intervention group, but not in the 36th week.

Also, Halse et al. (2015) found no significant difference in home-monitored capillary glucose levels in their intervention group, but there was a tendency toward lower

daily fasting glucose concentrations in the exercising group (P = 0.083). Furthermore, neither Bo et al., (2014), Brankston et al., (2004) or Avery et al., (1997) detected significant change in fasting glucose levels at the end of their trial. It seems that exercise has limited value in lowering fasting glucose during late stages of pregnancy. De Barros et al., (2010) measured fasting glucose level throughout the duration of the intervention, but they also reported no significant difference between the groups, although fasting glucose levels were slightly lower in the exercise group. In opposition to this, Davenport et al., (2008) and Jovanovic-Petersen et al., (1989) detected lower fasting capillary blood glucose levels ($P < 0.05$) in pregnant population on insulin therapy after their intervention, which consisted solely of regular walking.

However, the average of 3 postprandial measurements taken at the end of pregnancy was lower in the experimental group, with large effect size ($P < 0.001$, $d = 1.38$, $r = 0.57$). All participants were able to control their GDM with lifestyle changes and none of them needed pharmacological treatment. This is in accordance with the results from another trial (Halse et al., 2015) where overall postprandial glucose concentration was lower in the exercising group compared to the control group (P = 0.046). Likewise, four more previous trials (Bo et al., 2014; Davenport et al., 2008; Brankston et al., 2004; Jovanovic-Petersen et al., 1989) also reported a significant decrease of postprandial glucose levels at the end of their trial ($P < 0.001$; $P < 0.05$; $P < 0.05$). On the other hand, neither de Barros et al., (2010), Avery et al., (1997) nor Bung et al., (1991) reported any significant difference between groups in postprandial glucose values but they took into account average glucose values throughout the whole intervention. However, postprandial glucose values tended to be lower in the experimental group. Furthermore, in the trial performed by de Baross et al. (2010), the percentage of weeks spent within the target glucose range (80% of weekly capillary glucose measurements within preestablished guideline values) was higher (P = 0.006) when compared to the control group.

Lower postprandial glucose levels in the experimental group could have benefits and clinical significance for both the pregnant women and her fetus because of detrimental acute and long-term health effects of hyperglycaemia in pregnancy (Langer, Yogev, Most & Xenakis, 2005; Metzger, 2007; Metzger et al., 2008). The acute effects of exercise-induced decrease in blood glucose levels could account at least partially for the difference in postprandial concentrations. However, it is not

likely that this transient reduction could completely explain lower postprandial levels at the end of pregnancy as they could be the outcome of improved peripheral insulin sensitivity resulting from regular exercise.

Pre-pregnancy regular physical activity negatively correlated with fasting glucose level at the end of the pregnancy ($r_{pbi}$ = -0.429, P = 0.007). Lower weight gain between the 30th week of pregnancy and delivery positively affected postprandial glucose levels at the end of pregnancy ($r$ = 0.344, P = 0.034). Also, sport and exercise levels, measured by PPAQ, in the 30th and the 36th week of pregnancy were negatively correlated to postprandial glucose levels ($r$ = -0.527, P = 0.001; $r$ = -0.537, P = 0.001). Inactivity levels in the 36th week of pregnancy were positively correlated with postprandial glucose levels ($r$ = 0.369, P = 0.023).

None of our participants needed pharmacological therapy. Considering the fact that approximately 15% of women with GDM need to be treated with insulin or oral hypoglycaemic agents (Aswhal & Hod, 2015), we expected that 2 to 3 pregnant women from each group will need pharmacological treatment. However, all of them managed to achieve glycaemic targets only with diet and lifestyle changes. This is similar to the results from a previous study, performed by Jovanovic-Peterson et al. (1989), where none of the studied participants required insulin therapy. In the trial performed by de Barros et al. (2010), 56.3% the women from the control group and 21.9% women from the experimental group required insulin therapy. There was a significant statistical difference between groups (P = 0.005). On the other hand, in Bo et al. (2014) trial, less women required insulin therapy: 8.1% from the control group and 5.9% from the experimental group, with no significant difference between groups. All in all, only two women from both groups (10%) in the trial performed by Halse et al., (2015) required insulin therapy.

## 8.3 Impact of exercise programme on the rate of maternal complications during pregnancy

There were no complications during pregnancy in the experimental group, but also no significant difference between groups. We had two cases of pregnancy-induced hypertension and one of them progressed to preeclampsia in the control group. We were unable to confirm the hypothesis regarding the difference in the rate of

complications in pregnancy between the experimental and the control group. Other factors than physical activity could be related to these complications. Both pregnant women diagnosed with pregnancy-induced hypertension were older than 35, which is a risk factor for developing this condition. The pregnant woman who did not develop preeclampsia was also overweight, which is another risk factor for hypertension in pregnancy, and the woman who developed preeclampsia was a primigravida, which presents a risk factor for developing preeclampsia. Likewise, there could be other unknown factors, such as family history or underlying medical factors.

However, pregnancy induced hypertension positively correlated with postprandial glucose levels ($r_{pbi}$ = 0.345, P < 0.001), and negatively correlated with total activity levels, measured by PPAQ, in the 36th week of pregnancy ($r$ = -0.328, P = 0.044).

## 8.4 Impact of exercise programme on maternal weight gain and fat mass gain in pregnancy

The average weight gain in pregnancy is 12.5 kg (Hytten, 1991) and the proposed weight gain for healthy pregnant women with normal body mass is between 11 and 16 kg. Overweight pregnant women should not gain more than 11kg, and obese women not more than 9 kg (IOM, 2013). Our experimental group could be classified in normal weight category with the average BMI of 24.39 ± 4.89 kg/m$^2$, and our control group was slightly overweight (BMI = 25.29 ± 4.65 kg/m$^2$), but there was no significant difference between the groups (P = 0.515).

We were not able to confirm our hypothesis regarding the differences in weight gain and fat mass gain in pregnancy between the pregnant women who participated in our structured exercise programme and those who received only standard antenatal care. Excessive weight gain during pregnancy is a significant risk factor for development of T2DM after pregnancy.

The average weight gain during pregnancy was well within the recommended threshold for the experimental group, but the control group had a slightly higher weight gain than recommended. However, there was no significant difference between groups in overall weight gain or in body fat percentage. In the trial

conducted by Davenport et al., (2008) half of the studied population in both groups had excessive pregnancy weight gain.

Bo et al., (2014), Davenport et al., (2008) and Avery et al., (1997) also reported no significant difference in maternal body weight and BMI at the end of their intervention. However, their intervention was significantly different and included only daily walks. Neither de Barros et al., (2010) detected any significant changes regarding BMI at delivery and pregnancy weight gain between the groups. On the other hand, Artal et al. (2007) had a decreased total weight gain ($P < 0.01$) as well as the average weight gain per week ($P < 0.05$) in the experimental group.

## 8.5 Impact of exercise programme on labour outcomes

We were unable to confirm the initial hypothesis regarding the difference in the rate of complications during labour and delivery between the experimental and the control group. The timing of delivery was well within the term, between the 38th and the 40th week of pregnancy, in both groups. There were no premature labours, which confirms the safety of our exercise protocol and corresponds with the proven protective effect on pre-term delivery risk found by Mudd et al., (2013). None of the birth outcomes regarding the mode of birth and complications during labour and delivery were different for the experimental group. This is in accordance with the previous findings that maternal physical activity does not impact the mode of delivery (Ferraro et al., 2012). Previous trials on GDM population (Bo et al., 2014; de Barros, 2010; Davenport et al., 2008; Artal et al., 2007; Bung et al., 1991) also found no significant difference between groups in the rate of Caesarean sections, but Bo et al. (2014), reported a significant difference in the incidence of maternal complications during pregnancy, labour complications and neonatal complications ($P = 0.02$).

## 8.6 Impact of the exercise programme on neonatal outcomes

We were unable to confirm the initial hypothesis that there would be a significant difference regarding newborns' neonatal parameters and body mass between the experimental and the control group, in favour of the experimental group. We had excellent Apgar scores in both groups, as well as almost no complications affecting neonatal health. Exercise in pregnancy did not have any adverse effect on the fetus and neonatus, which is in accordance with previous findings (Nascimento et al., 2011; Barakat et al., 2011; Haakstad & Bø, 2011b).

There were no significant differences in neonatal weight, length and PI, but contrary to our expectations, neonatal BMI was sligthly higher in the experimental group (P = 0.035). Findings from previous trials indicate that there is no significant difference in neonatal weight (de Barros et al., 2010; Davenport et al., 2008; Artal et al., 2007; Avery, 1997; Bung et al., 1991). This is also opposite to the previous conclusions that children of exercising women are lighter and leaner at birth in comparison with non-exercising women (Clapp, 1996; Hopkins et al., 2010). However, we did not assess neonatal body composition and body fat percentage. Still, neonatal body mass in both groups was well within healthy limits. We had no macrosomia in any of the groups.

Higher intensity of exercise positively affected neonatal body weight and BMI, since we found a negative correlation between exercise intensity and neonatal body weight ($r$ = -0.481, P = 0.043) and BMI ($r$ = -0.469, P = 0.05).

There was a positive correlation between the gestational week of establishing the diagnosis and neonatal BMI ($r$ = 0.340, P = 0.037). This could speak in favour of an earlier diagnosis, because pregnant women who receive it have more time to adjust their diet and levels of physical activity to act preventively on newborn’s body size in order to avoid LGA and macrosomia.

## 8.7 Limitations and future research

The main limitation of the study is a small sample size. However, given the nature of the intervention, it would be highly impractical to perform individual exercise sessions on a larger sample of participants. Also, it was not easy to calculate an ideal sample size since there are no exact data on population size, i.e. the exact prevalence of GDM in the Croatian population according to the new criteria is still unknown. However, if we take into account that 93.8% of all births in Croatia happen in the age range between 20 and 40 years, there were 40091 births in Croatia in 2012 and the prevalence of GDM is assumed to be around 10.9% (there is no data for Croatia, but there is recent data for prevalence in the Italian population, which should be fairly similar to Croatian population) (Lacaria et al., 2014), the population size should be around 4201. This population size, given the confidence level of 95% and confidence interval of 10%, would require 94 participants to achieve an ideal sample size. Still, this was unfeasible because of the nature of the experimental intervention.

It is possible that the population studied for this thesis is not a representative sample of the general population affected by GDM. These pregnant women volunteered to participate in this trial and they might have been more aware of their condition and more committed to adhering to lifestyle changes and medical nutrition therapy. The fact that approximately 15% of women with GDM do not succeed in reaching glycaemic targets with diet only and require pharmacological treatment (Aswhal & Hod, 2015) supports this presumption, because none of the participants in our population needed pharmacological therapy. The study was also underpowered to find small differences in the incidence of adverse maternal and neonatal outcomes.

Another limitation of the study is not tracking and analysing dietary intake. However, all pregnant women received the medical nutrition intervention. Given the fact that the only difference between the groups was our intervention of exercise and daily walks, we feel that this is a reasonable limitation.

Future research should aim to compare aerobic and resistance exercise regimes. Also, the level of supervision could be compared in future research to determine an optimal level of supervision required to maintain adherence to protocol and to

achieve optimal health outcomes. Although high level of supervision probably improves participation in exercise, it also represents a significant cost to the healthcare system. Furthermore, effects of exercise programmes in pregnancy should be studied on T2DM and type I diabetes mellitus (T1DM) population because this has never been done. Long-term effects of exercise in pregnancy for diabetic population and their children should also be included in future research.

Also, aside from glucose levels, the effect of exercise on other laboratory values should be studied. These include C-reactive protein, adiponectin, resistin, IL-6, IL-8 and other inflammatory markers as well as cholesterol, triglycerides and insulin resistance.

# 9 CONCLUSION

Pregnancy is a period in life when women often try to improve their lifestyle and exercise habits. This should be especially encouraged in pregnant women with GDM. Exercise has only recently been introduced as a possibility in the treatment of GDM due to the lack of knowledge on the risks of exercise in pregnancy and the lack of evidence from research.

Our experimental exercise regime was completely safe for the pregnant women involved in the trial. While fasting glucose levels at the end of the pregnancy were lower in the experimental group, but not significantly, postprandial glucose levels were significantly lower in the experimental group ($P < 0.001$), which proved one of our most important hypotheses. Hyperglycaemia in pregnancy causes detrimental acute and long-term health effects on both the pregnant women and her fetus.

We successfuly proved that exercise offers significant benefit for women with GDM. Likewise, a negative correlation between sport and exercise levels and postprandial glucose levels in the 30th and the 36th week of pregnancy, and a positive correlation between inactivity levels and postprandial glucose levels further proves that there are significant advantages of exercise and physical activity in pregnancy with respect to glucose levels. Furthermore, the fact that pregnancy induced hypertension happened only in the control group and it was positively correlated with postprandial glucose levels and negatively correlated with total activity levels in the 36th week of pregnancy should be taken very seriously for planning trials in the future.

We were not succesful in confirming our hypothesis regarding the differences in weight gain and fat mass gain in pregnancy. However, our control group had a slightly higher weight gain than recommended. Excessive weight gain in pregnancy is a proven risk factor for the development of T2DM postpartum. There were no differences between groups regarding the mode of delivery and complications during labour and delivery, but this was in accordance with the previous trials. Likewise, there were no differences in neonatal parameters between groups. However, higher intensity of exercise negatively correlated with neonatal body weight and BMI.

Our adherence to the protocol was very high, probably because exercise sessions were individually tailored to each women, and participants could chose the time and days of the week to attend exercise sessions, which removed some of the barriers to exercising in pregnancy. Also, the women were able to see acute changes in their blood glucose levels before and after exercise, which further convinced them to continue with exercise.

Considering the fact that diabetes mellitus, especially T2DM, and obesity are assuming epidemic proportions worldwide, increased incidence of GDM is to be expected, along with its short- and long-term adverse effects on maternal and children's health. Therapeutic exercise during pregnancy might be an effective, safe and economically acceptable method for treatment of GDM, along with other lifestyle measures. This could help to avoid pharmacological therapy. Specific guidelines for the optimal type, frequency, duration and intensity of exercise for GDM should be developed and incorporated into general guidelines for the treatment of GDM.

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# POVZETEK V SLOVENSKEM JEZIKU

# 1 UVOD

Nosečnost je edinstveno stanje, ki je povezano z precejšnjimi fiziološkimi in psihološkimi spremembami, ki lahko spodbujajo sedentarni način življenja na sploh in/ali nizko stopnjo telesne aktivnosti pri ženskah. (Symons Downs, Chasan-Taber, Evenson, Leiferman & Yeo, 2012). V preteklosti je bilo nosečnicam priporočano, da omejijo stopnjo telesne aktivnosti vendar se v zadnjem času telesno aktivnost v nosečnosti obravnava kot preventivo pred različnimi kroničnimi boleznimi (American College of Sports Medicine, 2006). Dan danes je telesna aktivnost del prenatalne nege in najnovejše smernice (ACOG, 2002; Davies, Wolfe, Mottola, MacKinnon & Society of Obstetricians and Gynecologists of Canada, SOCG Clinical Practice Obstetrics Committee, 2003) proaktivno kažejo pozitiven vpliv telesne aktivnosti med nosečnostjo.

## 1.1 Prilagoditev presnove med nosečnostjo

Nosečnost spremljajo številne anatomske, psihološke in biokemijske prilagoditve, ki se začnejo kmalu po zanositvi in se nadaljujejo v nosečnost (Hytten, 1991). Spremembe v presnovi glukoze, pa tudi maščobnih kislin, nastopijo vzporedno s povečanimi energijskimi potrebami matere in ploda (Kalhan, 2000).

Za normalno nosečnost je značilna blaga hipoglikemija na tešče in hiperglikemija ter hiperinzulinemija po obroku (Hytten, 1991). Da se ohrani dotok glukoze do ploda po obroku, se ustvari stanje inducirane inzulinske rezistence. Povečano izločanje inzulina med nosečnostjo je najverjetneje odziv za kompenzacijo napredujoče inzulinske rezistence.

Ena od najbolj opaznih in stalnih sprememb presnove maščob med nosečnostjo je hiperlipidemija. Spremembe presnove lipidov povzročijo večanje materinih maščobnih zalog v začetku in sredini nosečnosti. Prevelike odlage maščobe imajo lahko negativen vpliv tako na mater kot na plod.

Zaradi presnovnih sprememb med nosečnostjo, predvsem znižane občutljivosti za inzulin, imajo nosečnice s prekomerno telesno maso in sedečim življenjskim slogom večje tveganje za disregulacijo presnove med nosečnostjo, predvsem za razvoj nosečniške sladkorne bolezni, preeklampsije in makrosomije ploda. Ženske s presnovnimi zapleti v nosečnosti imajo večje tveganje za presnovni sindrom kasneje v življenju. Okolje v maternici in presnovne motnje vplivajo tudi na razvoj ploda in imajo dolgotrajni vpliv na njegovo zdravje (El Hajj, Schneider, Lehnen & Haaf, 2014).

## 1.2 Vadba v nosečnosti

V zadnjih dvajsetih letih se značilno povečalo število raziskav o vplivu vadbe na zdravstveni status nosečnic in njihovih plodov. Številne študije dokazujejo blagodejne učinke vadbe v nosečnosti, kar je podprto tudi s trenutnimi smernicami o vadbi in zdravi nosečnosti. Na drugi strani, še vedno nimamo trdnih dokazil o vplivu vadbe ko so v nosečnosti prisotna patološka stanja kot so hipertenzija in sladkorna bolezen.

Trenutne smernice Ameriškega združenja ginekologov in porodničarjev (ACOG) (2002) priporočajo 30 ali več minut zmerne telesne aktivnosti večkrat na teden ali še bolje vsakodnevno (Nelson idr., 2007). Aerobna vadba, ki vključuje velike mišične skupine se priporoča za vzdrževanje srčnožilnega sistema, kot preventivo za kronične bolezni in pridobivanje telesne teže. Pred kratkim so Zavorski & Longo (2011) priporočili uporabo vadbe z obremenitvijo v splošni sistem vadbe za nosečnice.

# 2 NOSEČNIŠKA SLADKORNA BOLEZEN

Nosečniška sladkorna bolezen (NSB) je definirana kot kakršna koli intoleranca za ogljikove hidrate, ki se jo prvič diagnosticira v nosečnosti (Metzger idr., 2007). Predstavlja 90-95% vseh oblik sladkorne bolezni med nosečnostjo in je najpogostejši presnovni zaplet v nosečnosti (American Diabetes Association (ADA), 2015; Landon & Gabbe, 2011). Prevalenca NSB je do 14% (ADA, 2015; ACOG, 2013).

Hipoglikemija pri materi povzroči prekomeren transfer hranil plodu, predvsem glukoze, kar se odraža v hiperinzulinemiji pri plodu, ki še bolj povzroči nalaganje maščevja pri plodu, makrosomijo in komplikacije pri porodu (Jovanovic & Pettitt, 2001; Kjos & Buchanan, 1999). NSB je velik vzrok za obrojstveno obolevnost in smrtnost, tako kratkoročno kot dolgoročno (Ashwal & Hod, 2015). Povezana je z različnimi negativnimi izidi, tako za mater kot za plod.

Obstajajo različne koristi zdravljenja tudi blage NBS. Glavni cilj zdravljenja NBS je optimizirati glikemično kontrolo in izboljšati izide nosečnosti (Alwan idr., 2009). Po navadi kot prvotno terapevtsko strategijo za izboljšanje glikemične kontrole priporočamo spremembo načina prehranjevanja in življenjskega sloga (ACOG, 2012; National Institute for Health and Clinical Excellence (NICE), 2008). Če ta ukrep ne zagotovi ustrezne glikemične kontrola v 1 do 2 tednih, se uvede farmakološko terapijo. Kot del terapije je priporočljivo nadaljevati ali začeti s telesno vadbo zmerne intenzivnosti za vse nosečnice brez kontraindikacij (NICE, 2008; ACOG, 2013; ADA, 2015).

# 3 TELESNA VADBA IN SLADKORNA BOLEZEN TIPA 2

Sladkorna bolezen tipa 2 predstavlja globalni zdravstveni problem. Pri posameznikih, ki so sicer večino časa preživeli sedentarno, lahko že majhne količine gibalne/športne aktivnosti pozitivno vplivajo na markerje glukoze in presnovo maščob (Duncan idr., 2003). Gibalna/športna aktivnost vodi v izboljšanje metabolne kontrole, merjene z HbA1c, stopnje glukoze v krvi in občutljivosti na inzulin (Marwick idr., 2009). Mišično krčenje lahko, neodvisno od inzulina, izzove gibanje GLUT4 glukoznega transporterja v plazmo membrane (Ploug & Ralston, 2002).

Skoraj vse vrste gibalne/športne aktivnosti izboljšajo porabo glukoze in inzulinsko rezistenc, tako da zmanjšajo bazalni inzulin ter krvnega sladkorja v času 2–72h po zadnji vadbeni uri, izboljšujejo porabo glukoze in občutljivost na inzulin, kar je odvisno od trajanja in intenzivnosti gibalne/športne aktivnosti ter naknadno zaužite hrane (King idr., 1995; Boulé, Haddad, Kenny, Wells & Sigal, 2001; O'Gorman idr.,

2006). Priporočila o gibalni/športni aktivnosti za posameznike s sladkorno boleznijo tipa 2, so podobna tistim, ki so namenjena zdravi populaciji (Haskell idr., 2007). Priporočeno je, da se pacienti najmanj 210 min tedensko ukvarjajo z zmerno intenzivno gibalno/športno aktivnostjo ali 125 min tedensko z visoko intenzivno gibalno/športno aktivnostjo. Posamezna vadbena ura naj združuje tako vaje vzdržljivosti, kakor tudi vaje proti uporu.

# 4 VADBA IN NOSEČNIŠKA SLADKORNA BOLEZEN

Učinke gibalne/športne aktivnosti pred in med nosečnostjo, kot preventivo pred sladkorno boleznijo v nosečnosti, poročajo večinoma kohortne študije in majhno število randominiziranih kontrolnih študij, katerih rezultati so protislovni. Študije povezujejo višjo stopnjo gibalne/športne aktivnosti pred in med zgodnjo nosečnostjo, z nižjim tveganjem za razvoj sladkorne bolezni v nosečnosti (Tobias, Zhang, van Dam, Bowers & Hu, 2011). Gibalna/športna aktivnost je obenem tudi preventiva pred prekomerno pridobitvijo telesne mase med nosečnostjo, ki posredno vpliva na nastanek sladkorne bolezni v nosečnosti. Žal le približno 50% žensk, ki niso noseče, dosega priporočila o gibalni/športni aktivnosti, ta odstotek pa z zanositvijo še upada (Bauman, Ford & Armstrong, 2001).

Medtem ko je uporaba gibalne/športne aktivnosti v obravnavi sladkorne bolezni tipa 2, podprta z mnogimi dokazi, so le-ti, ko govorimo o učinkih na potek in izid sladkorne bolezni v nosečnosti, omejeni. Na tem področju je bilo izvedenih le 9 prospektivnih študij, od katerih je 7 randomoziranih kontrolnih študij (Jovanovic-Peterson, Durak & Peterson, 1989; Bung, Artal, Khodiguian & Kjos, 1991; Avery, Leon & Kopher, 1997; Brankston, Mitchell, Ryan & Okun, 2004; de Barros, Lopes, Francisco, Sapienza & Zugaib, 2010; Bo idr., 2014; Halse, Wallman, Newnham & Guelfi, 2015), 2 pa sta nerandomizirani (Artal, Catanzaro, Gavard, Mostello & Friganza, 2007; Davenport, Mottola, McManus & Gratton, 2008). Ne glede na različno metodologijo in majhne vzorce v posameznih študijah, je v večini le-teh, razlika v glikemični kontroli ali potrebi po inzulinski terapiji statistično značilna (Jovanovic-Peterson idr., 1989; Brankston idr., 2004; Bung idr., 1991; Davenport idr., 2008; de Barros idr., 2010; Bo idr., 2014; Halse idr., 2015).

# 5 CILJI DOKTORSKE DISERTACIJE

Namen doktorske disertacije je bil proučiti in dodati nova znanstvena dognanja o morebitnih učinkih povezanih z zdravjem same uporabe individualiziranega vodenega programa, ki sestoji iz aerobnih vaj in vaj proti dodatnem uporu, na nosečniško sladkorno bolezen. Osnovni cilj raziskave je bil ugotoviti kako ta program vadbe vpliva na potek in izide nosečnosti z NSB.

## 5.1 Hipoteze

Naslednje glavne hipoteze so bile razvite na osnovi ciljev:

H1: Obstajajo statistično pomembne razlike v glikemičnih parametrih med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno zdravstveno oskrbo

H2: Obstajajo statistično pomembne razlike v stopnji zapletov v obdobju nosečnosti med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno zdravstveno oskrbo

H3: Obstajajo statistično pomembne razlike v stopnji pridobljene telesne mase in maščobne mase v obdobju nosečnosti med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno zdravstveno oskrbo

H4: Obstajajo statistično pomembne razlike v stopnji zapletov med popadki in porodom med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno zdravstveno oskrbo

H4: Obstajajo statistično pomembne razlike v neonatalnih parametrih in telesni masi novorojenčkov med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno zdravstveno oskrbo

# 6 METODE IN MATERIALI

## 6.1 Zasnova raziskave in etika

Raziskava je bila zasnovana kot naključna kontrolirana raziskava. Raziskava je bila izvedena v okviru hrvaškega nacionalnega znanstvenega projekta Diabetes in metabolični sindrom po predhodnem gestacijskem diabetesu (št. 108-1080408-0385). Etična odobritev je bila pridobljena s strani vseh ustreznih organov in pisno dovoljenje prav tako s strani vseh udeležencev raziskave.

## 6.2 Preiskovanci

V raziskavi smo potencialno vključili nosečnice iz glavnega mesta Hrvaške in okoliških krajev, ki so bile diagnosticirane z NSB. Za diagnozo NSB so bila uporabljena IADPSG merila (Metzger idr., 2010). Merila za vključitev v raziskavo so bila: diagnoza nosečnostne sladkorne bolezni v skladu z merili IADPSG, starost med 20 in 40 in sposobnost branja, razumevanja in govora hrvaškega jezika. Merila za izključitev so bila: anamneza sladkorne bolezni in splavov, farmakološko zdravljenje s peroralnih antidiabetikov in/ali insulinom, uvedenih pred udeležbo v raziskavi, druga obstoječa bolezenska stanja in kontraindikacije za vadbo po ACOG (2002) merilih.

## 6.3 Ocene in meritve

Izhodiščni podatki so bili zabeleženi ob prvem obisku/intervjuju in so zajemali demografske podatke, anamnezo, morebitne kontraindikacije za vadbo, višino, težo na začetku nosečnosti, rezultate oralnog glukoznog tolerančneg testa (OGTT) in pregled zdravstvene kartoteke. V 30. tednu so bile izvedene antropološke meritve (telesne mase, obsegi rok ter kožne gube) s posebnim vprašalnikom (PPAQ). V 33. tednu so bile opravljene le antropološke meritve in v 36. tednu smo ponovili vse meritve in ocene opravljene v 30. tednu nosečnosti. Pri zadnjem intervjuju smo zbrali podatke o glikemčni kontroli v zadnjih tednih nosečnosti, porodu, neonatalno

zdravstveno stanje in antropometrične podatke. Podatki so bili pridobljeni iz zdravstvene kartoteke in poročila ob izpustu iz bolnišnice/porodnišnice.

Podatki OGTT in glukoze so bili analizirani v medicinskem biokemičnem laboratoriju v skladu s standardnimi za akreditirane laboratorije (ISO 15189 Medicinski laboratoriji - Posebne zahteve za kakovost in usposobljenost) in v skladu s priporočili hrvaške zbornice medicinskih biokemikov (Vučić Lovrenčič, Honovic, Kralik & Matica, 2012). V naše končne analize smo vzeli nosečničine izvide stanja glukoze, ki so bili analizirani med 38. in 40. tednom nosečnosti.

## 6.4 Intervencija

Nosečnice v eksperimentalni skupini so bile vključene v individualizirane programe vadbe dvakrat tedensko, poleg že obstoječih postopkov obravnave. Trajanje programov vadbe je bilo 50-55 minut na izveden trening. Nosečnice so izvajale minimalno 30 min visoko intenzivne hoje na dan, priporočeno je bilo takoj za po obroku. Preiskovanke v eksperimentalni skupini so začele vadbene procese takoj za postavljeno diagnozo NSB in vadile so skozi celotno obdobje nosečnosti. Vse preiskovanke so bile vključene v medicinsko prehransko terapijo (MPT) za nosečnice z NSB.

Program vadbe je bil razvit v skladu z veljavnimi smernicami za vadbo v obdobju nosečnosti (ACOG, 2002; RCOG, 2006). Program vadbe je bil sestavljen iz aerobne vadbe (20 minut), vadbe proti dodatnem uporu (20-25 minut), vaj za krepitev medeničnega dna, razteznih vaj in vaj za sprostitev (10 minut).

Več meritev je bilo opravljenih pred, med in po vadbi. Srčni utrip (HR) matere je bil pod stalnim nadzorom. Poleg tega so bile vrednosti arterijskega krvnega tlaka, temperature bobniča in srčnega utripa ploda zabeležene pred vadbo, po aerobnem delu vadbe, po vadbi proti dodatnem uporu in na koncu same vadbe. Vzorce kapilarne krvi smo odvzeli trikrat za testiranje ravni glukoze in dvakrat za testiranje nivoja laktatov pred in po vadbi proti dodatnem uporu.

## 6.5 Statistične analize

Statistične analize so bile izvedene s pomočjo programa SPSS 19.0 (IBM, Armonk, NY, ZDA). Opisna statistika je bila opravljena za vse spremenljivke. Shapiro-Wilkonov test smo uporabili za preverjanje normalnosti podatkov in Levene-ov test za preverjanje homogenosti varianc. Kadar so bile izpolnjene predpostavke normalnosti in homogenosti varianc, smo spremenljivke analizirali s pomočjo T-testa. Nenormalno porazdeljene in kategorične podatke smo analizirali z Mann-Whitney U testom. Stopnja povezanosti med spremenljivkami je bila izračunana s Pearsonovim korelacijskim koeficientom ($r$) in točkovnim biserialnim korelacijskim koeficientom ($r_{pbi}$). Stopnja, pri kateri smo sprejemali/zavračali hipoteze je bila določena pri P <0,05. Cohen d ($d$) in velikost učinka ($r$) smo izračunali za vse spremenljivke, prav tako pri stopnji $p \leq 0,05$.

# 7 REZULTATI

Skupaj je 42 nosečnic z diagnozo nosečniške sladkorne bolezni vključeno in randomizirane v raziskavo. Razdeljene so bile v dve skupini, 20 v eksperimentalno in 22 nosečnic v kontrolno skupino. Štiri merjenke (9,52%) so odstopile, dve iz eksperimentalne skupine (10%) in dve iz kontrolne skupine (9,09%). Eksperimentalna in kontrolna skupina sta bili podobni, brez začetnih statistično značilnih razlik (P > 0,05).

## 7.1 Karakteristike vadbe

V času raziskave je skupaj izvedenih 365 vadbenih enot, 20,28 ± 7,68 vadbenih enot na preiskovanko. Minimalno število treningov po merjenki je bilo 12 in maksimalno 34. Povprečna realizacija vadbenega protokola glede na načrt je bila visoka (84,22%), nad pragom 70%. Po aerobnem del uso ugotovljene spremembe pri srčni frekvenci matere in ploda kot tudi na telesni temperaturi matere (P < 0,001), kot tudi pri srčni frekvenci matere in ploda (P = 0,003) pri vadbi proti uporu. Kapilarna raven glukoze je značilno padla glede na začetno vrednost (P < 0,001). Raven laktata je značilno zrasla glede na začetno vrednost (P < 0,001).

Spremembe sistoličnega in diastoličnega krvnega tlaka se niso značilno spremenile v času izvajanja vadbe kot tudi po končani vadbi.

Vse nosečnice iz eksperimentalne skupine so imele nalogo da vsak dan hitro hodijo, najmanj 30 minut in da vodijo dnevnik opravljene vadbe. Ta del intervencije je imel 100% realizaciju protokola, kar je odlično in je značilno nad 70%, s povprečnim odstotkom 95,56 ± 4,54% realizacije načrtovanega programa.

## 7.2 Vprašalnik Physical Activity in Pregnancy (Telesna aktivnost nosečnic)

Najbolj značilna razlika, z velikim efektom učinka je bila na ravni športnih aktivnosti. V obdobju 30. tedna ($P < 0,001$, $d = 2,37$, $r = 0,76$), kot tudi v obdobju 36. tedna nosečnosti ($P < 0,001$, $d = 2,41$, $r = 0,77$), so nosečnice iz eksperimentalne skupine imele značilno višjo raven športne dejavnosti glede na kontrolno skupino. Tudi aktivnosti zmerne intenzivnosti ($P = 0,016$, $d = 0,63$, $r = 0,30$) in aktivnosti transporta ($P = 0,024$, $d = 0,82$, $r = 0,38$) so bile značilno različne v 36. tednu nosečnosti v korist eksperimentalne skupine.

## 7.3 Parametri glikemične kontrole

Nobena od preiskovank iz obeh skupin ni potrebovala farmakološko zdravljenje (inzulin in/ali oralne hipoglikemike). Povprečna raven glukoze na tešče je bila nižja v eksperimentalni skupini, vendar to ni bilo statistično značilno ($P = 0,367$). Na drugi strani, povprečje od treh postprandijalnih meritev ravni glukoze je bilo značilno nižje v eksperimentalni skupini, z velikim efektom učinka ($P < 0,001$, $d = 1,38$, $r = 0,57$).

## 7.4 Zapleti v nosečnosti

Zapleti v nosečnosti so bili redki. Noben zaplet se ni zgodil v eksperimentalni skupini, niti ni bilo značilnih razlik med skupinama.

## 7.5 Pridobivanje na telesni masi in rast odstotka telesne maščobe

Zaznali smo nekaj manjših razlik med skupinama glede na telesno težo, odstotek telesne maščobe in porast telesne teže tekom specifičnih časovnih točk v nosečnosti, vendar nobena od teh razlik ni bila značilna.

## 7.6 Zapleti pri porodu

Čeprav je eksprimentalna skupina imela zgodnejši začetek poroda, ni bilo značilnih razlik med skupinama v trenutku začetka poroda in so vse merjenke rodile med 38. in 40. tednom nosečnosti, brez primerov zgodnjega poroda. Bilo je več indukcij poroda v kontrolni skupini, vendar brez značilne razlike, obenem ni bilo značilnih razlik v številu podaljšanih porodov, instrumentalnih porodov in carskih rezov.

## 7.7 Neonatalni parametri

Ni bilo slabih rezultatov in resnih neonatalnih komlikacij po porodu, kot tudi ni bilo pojavov makrosomije in neonatalne hipoglikemije. Apqar ocene so bile brez značilnih razlik kot tudi število neonatalnih komplikacij. Neonatalna teža, dolžina in ponderalni indeks so bili tudi brez značilnih razlik med skupinama. Kljub temu obstaja značilna razlika v neonatalnem indeksu telesne mase, kateri je bil nekoliko višji v eksperimentalni skupini, vendar z zmernim efektom učinka ($P = 0,035$, $d = -0,76$, $r = -0,35$).

# 8 RAZPRAVA

Disertacija je sestavljena iz treh glavnih področjih. Prvo, raziskuje vpliv programa vadbe na zdravje nosečnice med nosečnostjo, skupaj z rezultati poroda. Drugo, raziskuje vpliv vadbe na zdravje novorojenčkov. Končno, raziskuje pridobivanje telesne teže nosečnice v času nosečnosti, vključno s spremembami odstotka telesne maščobe. Dodatno smo želeli preučiti akutne učinke vadbe programa na več

fizioloških parametrov, da bi ocenili splošno varnost intenzivnosti vadbe, trajanje in pogostost.

Kolikor nam je znano, je to prva študija katera raziskuje kombinacijo aerobne vadbe in vadbe proti uporu za ženske z NSB. Poleg tega to je druga študija o vplivu individualnega programa vadbe na populacijo z NSB, in prvi, ki raziskuje učinek individualnih programov vadbe te vrste. Podatki iz te študije predstavljajo najbolj celovite podatke o akutnih učinkih vadbe na populacijo z NSB.

## 8.1 Akutni učinki vadbe

Med treningom se niso pojavljali opozorilni znaki, ki bi zahtevali prenehanje vadbe. Poleg tega ni bilo nobenih škodljivih učinkov zaradi telesne vadbe. Povprečje protokola telovadbe je bilo zelo visoko, 84,22%. Treningi so povzročili pomembne fiziološke spremembe, glede na povprečni srčni utrip, fetalni srčni utrip, telesno temperaturo, kapilarno razino glukoze in laktata v kri. Povprečje intenzivnosti v času obeh delov treninga, aerobnog in proti uporu, je bila 65,06 ± 4,42% od maksimalnega srčnega utripa, in je ohranila vrednost 13-14 na Borgovi lestvici subjektivnega občutka obremenitve.

Povprečna fetalna srčna frekvenca pred začetkom vadbe je bila 141,17 ± 5,90, ki se je povečala na 150,1 ± 5,8 po aerobnem delu, oziroma 6,34% oziroma 9 udarcev na minuto. Najvišja zabeležena vrednost fetalnega srčnega utripa po aerobni vadbi je 163 utripov na minuto. Povprečna fetalna srčna frekvenca po vadbi proti uporu je bila 145,2 ± 6,5, kar je glede na izhodiščno vrednost zvišano za 2,89% ali 4,1 udarcev na minuto. Ni bilo znižanja fetalnega srčnega utripa pod izhodiščne vrednosti. Ti rezultati so podobni rezultatom iz prejšnjih študij (Avery idr., 1997), kjer je bilo zabeleženo zvišanje fetalnega srčnega utripa za 10 udarcev na minuto glede na izhodiščne vrednosti pred vadbo, ki je trajala povprečno 10 minut pri 40% intenzivnosti.

Kapilarna glukoza se je občutno zmanjšala ($P < 0,001$) v primerjavi z izhodiščnimi vrednostmi, katere so bile v povprečju 4,70 ± 0,56 mmol/L, a padle so na 3,92 ± 0,38 mmol/L; oziroma, padla je za 16,6%. To je v skladu s prejšnjimi rezultati kako izkoriščanje glukoze v mišicah med vadbo zmernega inteziteta preseže proizvodnjo

glukoze v jetrih kaj povzroči upad razine glukoze v kri med aktivnostjo (Minuk idr., 1981) Koncentracija laktata se je povečala ($P < 0,001$) od 1,48 ± 0,65 mmol/L do 3,17 ± 1,36 mmol/L, kar je zvišanje vrednosti za 114,2%.

## 8.2 Vpliv programov vadbe na nadzor glikemije

Uspešno smo potrdili našo hipotezo o parametrih glikemičnega nadzora, vendar le deloma. Obstajal je trend, da so koncentracije glukoze na tešče ob koncu nosečnosti, med 38 in 40 tednov, bile nižje v eksperimentalni skupini, ampak ni bilo značilne razlike ($P = 0,367$). Ta rezultat je podoben rezultatom predhodnih študij, vendar povprečna vrednost treh postprandialnih merjenj na koncu nosečnosti je bila bistveno manjša v eksperimentalni skupini, z velikim efektom učinka ($P < 0,001$, $d = 1,38$, $r = 0,57$). To je v skladu z rezultati druge preiskave (Halse idr., 2015), kjer je bila povprečna postprandialna koncentracija glukoze bistveno nižja v skupini vadbe v primerjavi s kontrolno skupino ($P = 0,046$). Prav tako štiri prejšnje študije (Bo idr., 2014; Davenport idr., 2008; Brankston idr., 2004; Jovanovic-Petersen idr., 1989) so poročale tudi o precejšen upadu postprandialne koncentracije glukoze na koncu študije ($P < 0,001$; $P < 0,05$; $P < 0,05$).

Nižje postprandijalne koncentracije glukoze v eksperimentalni skupini, bi lahko imele pozitiven učinek in klinični pomen tudi za nosečnice, tudi za njen fetus zaradi neugodnih akutnih in dolgoročnih zdravstvenih posledic hiperglikemije v nosečnosti (Langer, Yogev, Most & Xenakis, 2005; Metzger, 2007; Metzger idr., 2008). Akutni učinek zmanjšanja koncentracije glukoze v krvi zaradi vadbe se lahko delno pripiše razliki v postprandialnim koncentracijami. Vendar pa ni verjetno, da bi to prehodno zmanjšanje lahko v celoti pojasnili z nižjim postprandialnim koncentracijami ob koncu nosečnosti in je možno, da je to posledica izboljšane periferne občutljivosti na insulin kot je rezultat redne vadbe.

## 8.3 Učinek programa vadbe na pojavnost zapletov med nosečnostjo

Med nosečnostjo v eksperimentalni skupini ni bilo nobenih zapletov, pa tudi ni bilo bistvene razlike med skupinami. Nismo mogli potrditi hipotezo o pogostosti razlik komplikacij nosečnosti med eksperimentalno in kontrolno skupino.

## 8.4 Učinek programa vadbe na pridobivanje telesne mase in pridobivanje telesne maščobe v nosečnosti

Naša eksperimentalna skupina se lahko razvršča v kategorijo normalne teže, z indeksom telesne mase (ITM) 24,39 ± 4,89 kg/m$^2$, in naša kontrolna skupina je imela nekoliko prekomerno telesno težo (ITM = 25,29 ± 4,65 kg/m$^2$) vendar pa ni bilo značilnih razlik med skupinama (P = 0,515). Nismo mogli potrditi našo hipotezo o razliki v njihovem pridobivanju telesne teže in telesne maščobe med nosečnostjo med nosečnicami, ki so sodelovale v strukturiranem programu vadbe in tistih, ki so prejemale samo standardno antenatalno nego.

Bo idr. (2014), Davenport idr. (2008), Avery idr. (1997) in de Barros idr. (2010), prav tako niso poročali o nobenih pomembnih razlik v telesni masi nosečnice in indeksu telesne mase na koncu raziskave. Po drugi strani pa Artal idr. (2007) so imeli bistveno zmanjšanje telesne mase (P < 0,01) in povprečno povečanje telesne mase na teden (P < 0,05) v eksperimentalni skupini.

## 8.5 Učinek programa vadbe na izid poroda

Nobeden od izidov poroda glede na način poroda in zapletov med porodom se niso bistveno razlikovali za eksperimentalno skupino. To je v skladu s prejšnjimi rezultati ki nosečnična telesna aktivnost ne vpliva na način poroda (Ferraro idr., 2012). Prejšnje raziskave na populaciji nosečnic z NSB (Bo idr., 2014; de Barros idr., 2010; Davenport idr., 2008; Artal idr., 2007; Bung idr., 1991), prav tako niso

ugotovile pomembnih razlik med skupinami v pojavnosti carskega reza, ali Bo idr. (2014) so poročali o značilnih razlikah v splošni incidenci komplikacij katere vključujejo komplikacije med nosečnostjo, porodom in neonatalne komplikacije (P = 0,02).

## 8.6 Učinek programa vadbe na neonatalne rezultate

Ni bilo pomembnih razlik v neonatalni teži, dolžini in ponderalnom indeksu. Vendar nasprotno našim pričekovanjima neonatalni indeks telesne mase je bil v nasprotju z našimi pričakovanji, neonatalni index je bil višji v eksperimentalni skupini (P = 0,035). Rezultati iz prejšnjih študij, so pokazali, da ni bistvene razlike v neonatalni teži (de Barros idr., 2010;. Davenport idr., 2008;. Artal idr., 2007; Avery idr., 1997; Bung idr., 1991). To je tudi v nasprotju s prejšnjimi rezultati, da so otroci nosečnic, ki izvajajo vadbo rojeni lažji in z nižjim odstotkom telesne maščobe v primerjavi z otroci nosečnic, ki ne vadijo (Clapp, 1996; Hopkins idr., 2010). Kljub temu je neonatalna telesna teža pri obeh skupinah v normalnem območju. Makrosomije ni bilo v nobeni izmed skupin.

## 8.7 Omejitve in prihodnje raziskave

Glavna omejitev raziskave je majhen vzorec preiskovancev. Vendar pa je glede na naravo posega zelo nepraktično uporabiti individualne treninge na večjem vzorcu preiskovancev. Poleg tega je možno, da je testirana populacija nereprezentativni vzorec splošne populacije prizadete s gestacijskim diabetesom. Druga omejitev raziskave je da ne spremlja in analizira vnos hranil. Vendar pa so vse ženske bile na medicinski prehrani.

Prihodnje raziskave bo potrebno usmeriti v primerjavo učinkov aerobne vadbe in vadbe proti uporu. Prav tako je potrebno primerjati stopnjo nadzora vadbe za določitev optimalne ravni nadzora potrebne za skladnost s protokolom in doseganja optimalnih zdravstvenih rezultatov. Dolgoročni učinki vadbe med nosečnostjo pri sladkornih populaciji in njihovih otrok tudi treba vključiti v prihodnjih študijah. Potrebno je tudi poleg ravni glukoze v krvi raziskati vpliv vadbe na druge laboratorijske vrednosti.

# 9 ZAKLJUČEK

Zaradi pomanjkanja znanja o tveganjih telesne vadbe v nosečnosti, kot tudi zaradi premalo znanstvenih izsledkov je telesna vadba šele pred kratkim predstavljena kot možnost pri zdravljenju NSB. Naš eksperimentalni program vadbe je bil za nosečnice vključene v raziskavo varen. Raven glukoze na tešče, na koncu nosečnosti je bil nižji pri eksperimentalni skupini vendar ne značilno, raven postprandialne glukoze je bil značilno višji v eksperimentalni skupini ($P < 0,001$), s čem smo potrdili osnovno hipotezo. Hipoglikemija v nosečnosti povzroča škodljive akutne in dolgoročno zdravstvene posledice za nosečnicu kot tudi za plod.

Negativna korelacija med ravnjo športne aktivnosti in postprandialne ravni glukoze v 30. in 36. tednu nosečnosti ter pozitivne korelacije med ravnjo neaktivnost in postprandialne ravni glukoze dokazuje obstoj značilnih koristi telesne vadbe in telesne aktivnosti v nosečnosti glede na raven glukoze. Glede na razlike v povečanju telesne mase in odstotka maščobe v telesu nismo potrdili hipotezo, ali je kontrolna skupina imela povečanje v večji meri od priporočil.

Terapevtska vadba v nosečnosti bi lahko bila učinkovita, varna in ekonomsko sprejemljiva metoda za terapijo NSB, skupaj z drugimi prilagoditvami vezano na življenski slog. Potrebno je razviti specifične smernice za optimalno vrst, frekvenco, trajanje in intenzivnost vadbe za NSB ter jih vpeljati v splošne smernice oz priporočila za zdravljenje NSB.

# APPENDICES

**Appendix 1:** Study approval by the Ethics Committee, University Hospital Centre Zagreb.

**KLINIČKI BOLNIČKI CENTAR ZAGREB**
**Etičko povjerenstvo**
**Z A G R E B - Šalata 2**

Klasa: 8.2.-12/125-2
Broj: 02/21-LJH
Zagreb, 03. prosinca 2012.

**Iva Šklempe Kokić**
**B.Berse I/50**
**43000 Bjelovar**

**Predmet: Suglasnost za provođenje istraživanja u svrhu izrade doktorske disertacije**

Na sjednici Etičkog povjerenstva KBC-a Zagreb održanoj 20. studenog 2012. godine razmotrena je zamolba Ive Šklempe Kokić, za odobrenje provođenja istraživanja pod nazivom „Utjecaj terapijskog vježbanja za ishod i tijek gestacijskog dijabetesa mellitusa."

Etičko je povjerenstvo suglasno s provođenjem navedenog istraživanja, s obzirom da se isto ne kosi s etičkim načelima.

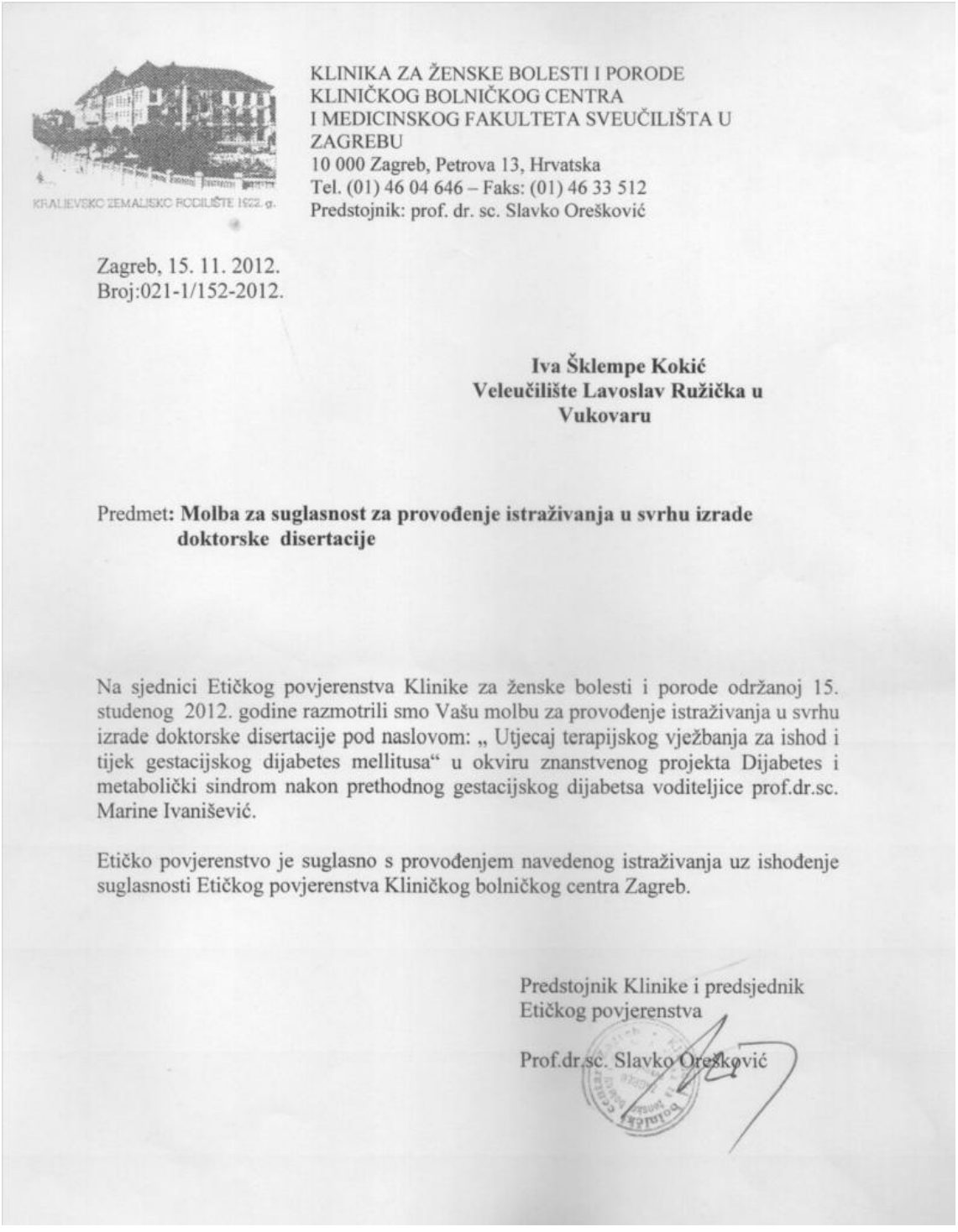
**Predsjednik Etičkog povjerenstva**

**Prof.dr.sc. Daniel Derežić**

Dostavljeno:

1. Arhiva.
2. Iva Šklempe Kokić

**Appendix 2:** Study approval by the Ethics Committee, Department of Gynaecology and Obstetrics, University Hospital Centre Zagreb.



KRALJEVSKO ZEMALJSKO PODILIŠTE 1922. g.

KLINIKA ZA ŽENSKE BOLESTI I PORODE
KLINIČKOG BOLNIČKOG CENTRA
I MEDICINSKOG FAKULTETA SVEUČILIŠTA U ZAGREBU
10 000 Zagreb, Petrova 13, Hrvatska
Tel. (01) 46 04 646 – Faks: (01) 46 33 512
Predstojnik: prof. dr. sc. Slavko Orešković

Zagreb, 15. 11. 2012.
Broj:021-1/152-2012.

**Iva Šklempe Kokić**
**Veleučilište Lavoslav Ružička u Vukovaru**

Predmet: **Molba za suglasnost za provođenje istraživanja u svrhu izrade doktorske disertacije**

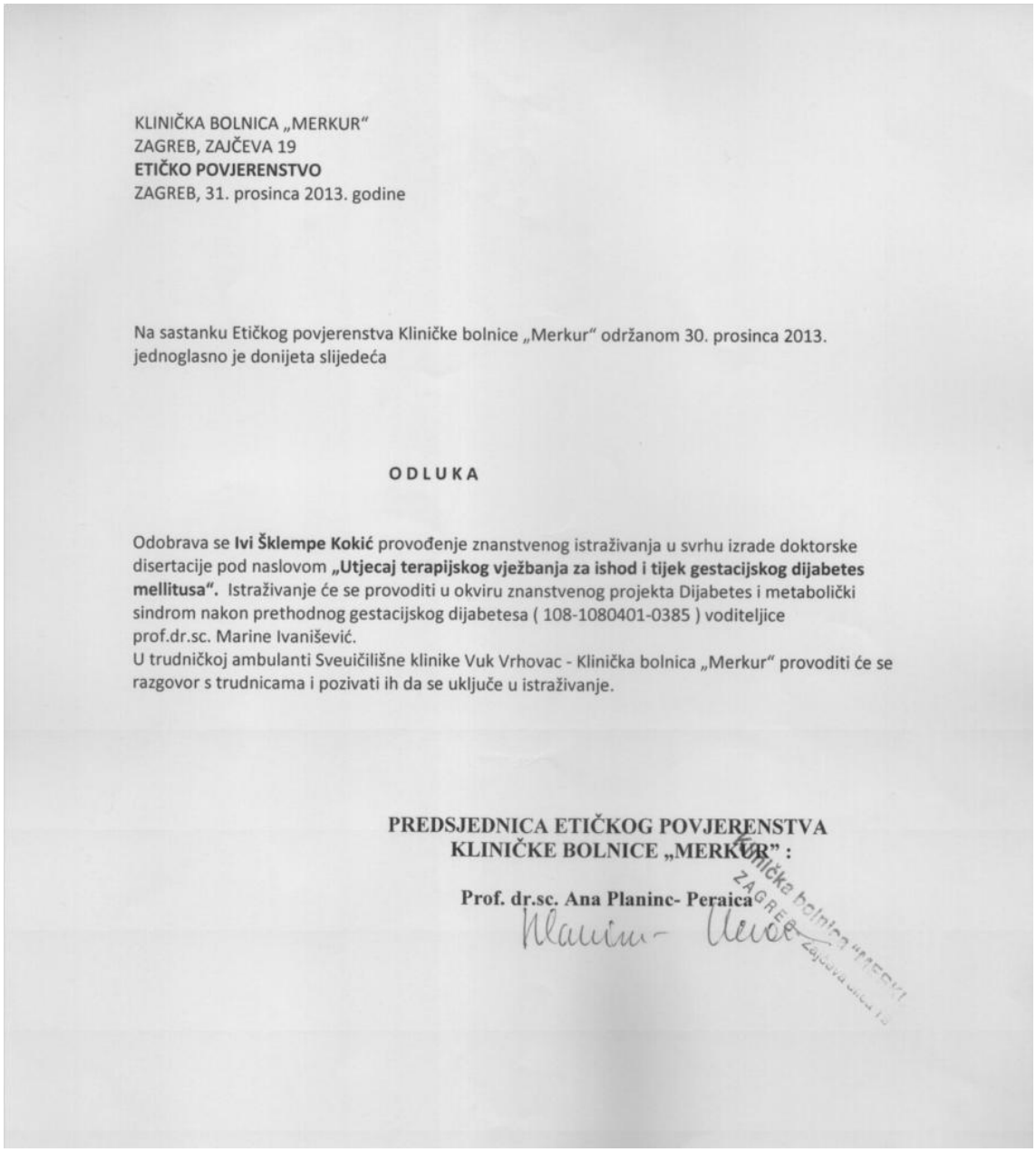
Na sjednici Etičkog povjerenstva Klinike za ženske bolesti i porode održanoj 15. studenog 2012. godine razmotrili smo Vašu molbu za provođenje istraživanja u svrhu izrade doktorske disertacije pod naslovom: „ Utjecaj terapijskog vježbanja za ishod i tijek gestacijskog dijabetes mellitusa“ u okviru znanstvenog projekta Dijabetes i metabolički sindrom nakon prethodnog gestacijskog dijabetsa voditeljice prof.dr.sc. Marine Ivanišević.

Etičko povjerenstvo je suglasno s provođenjem navedenog istraživanja uz ishođenje suglasnosti Etičkog povjerenstva Kliničkog bolničkog centra Zagreb.

Predstojnik Klinike i predsjednik
Etičkog povjerenstva

Prof.dr.sc. Slavko Orešković

**Appendix 3:** Study approval by the Ethics Committee, University Hospital Merkur



KLINIČKA BOLNICA „MERKUR"
ZAGREB, ZAJČEVA 19
**ETIČKO POVJERENSTVO**
ZAGREB, 31. prosinca 2013. godine

Na sastanku Etičkog povjerenstva Kliničke bolnice „Merkur" održanom 30. prosinca 2013. jednoglasno je donijeta slijedeća

**ODLUKA**

Odobrava se **Ivi Šklempe Kokić** provođenje znanstvenog istraživanja u svrhu izrade doktorske disertacije pod naslovom **„Utjecaj terapijskog vježbanja za ishod i tijek gestacijskog dijabetes mellitusa".** Istraživanje će se provoditi u okviru znanstvenog projekta Dijabetes i metabolički sindrom nakon prethodnog gestacijskog dijabetesa ( 108-1080401-0385 ) voditeljice prof.dr.sc. Marine Ivanišević.
U trudničkoj ambulanti Sveučilišne klinike Vuk Vrhovac - Klinička bolnica „Merkur" provoditi će se razgovor s trudnicama i pozivati ih da se uključe u istraživanje.

**PREDSJEDNICA ETIČKOG POVJERENSTVA**
**KLINIČKE BOLNICE „MERKUR" :**

**Prof. dr.sc. Ana Planinc- Peraica**

**Appendix 4:** Written permission to use PPAQ questionnaire.


Hi Iva:
Please find the PPAQ and instructions for its use attached.
Best of luck with your research.
Thanks.
Lisa

--
**********
Lisa Chasan-Taber, Sc.D.
Professor of Epidemiology
Division of Biostatistics & Epidemiology
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405 Arnold House
715 North Pleasant Street
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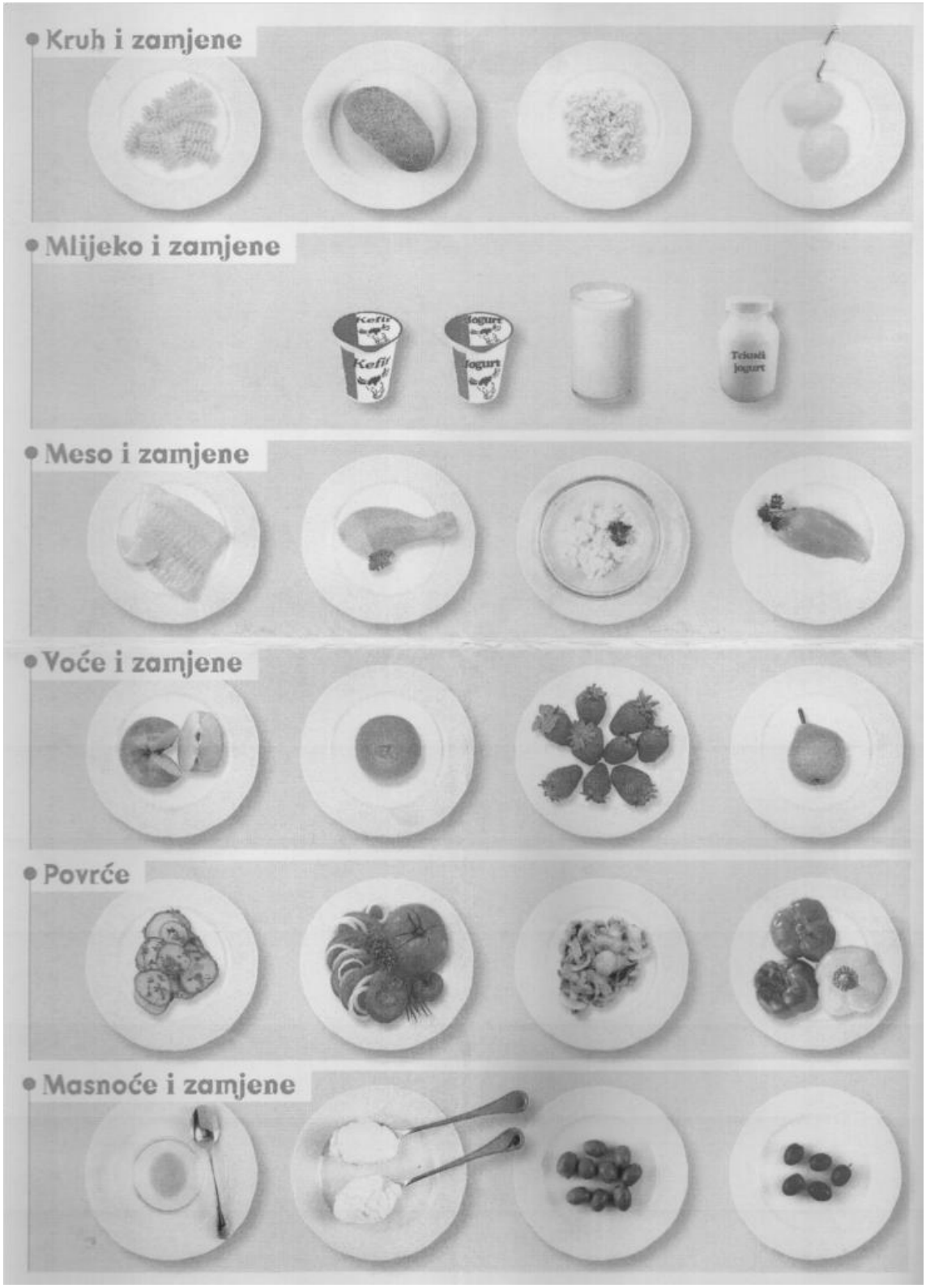
Amherst, MA 01003-9304

tele: 413-545-1664
fax: 413-545-1645
email: LCT@schoolph.umass.edu
website: http://people.umass.edu/lisact/
**********

**Appendix 5:** Medical nutrition therapy characteristics and instructions from the Referral Centre for Diabetes, University Clinic for Diabetes, Endocrinology and Metabolic Diseases Vuk Vrhovac, University Hospital Merkur.

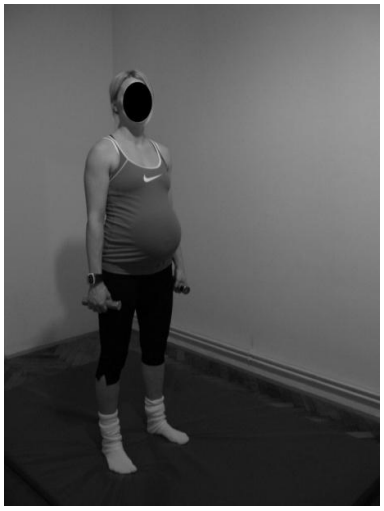

Kruh i zamjene
Mlijeko i zamjene
Meso i zamjene
Voće i zamjene
Povrće
Masnoće i zamjene

**Appendix 6:** Resistance exercise protocols.

Protocol 1

Exercise 1

Starting position



Semi-squat with free weights

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 2

Starting position

Alternating reciprocal leg extension and arm flexion from quadruped position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 3

Starting position

Bilateral arm abduction with theraband

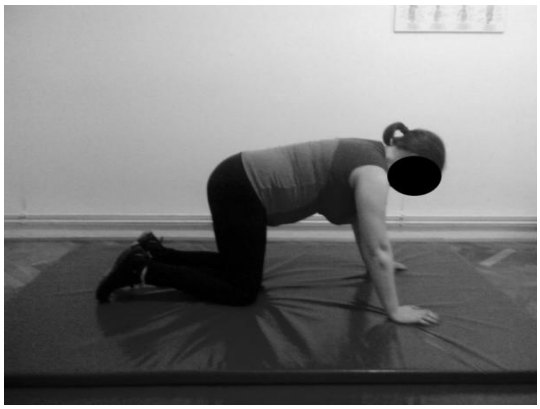
*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 4

Starting position



Leg abduction from quadruped position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 5

Starting position

Leg abduction from side-lying position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 6

Starting position

„Bridge" (pelvis elevation from supine position)

*Photo: Iva Šklempe Kokić*

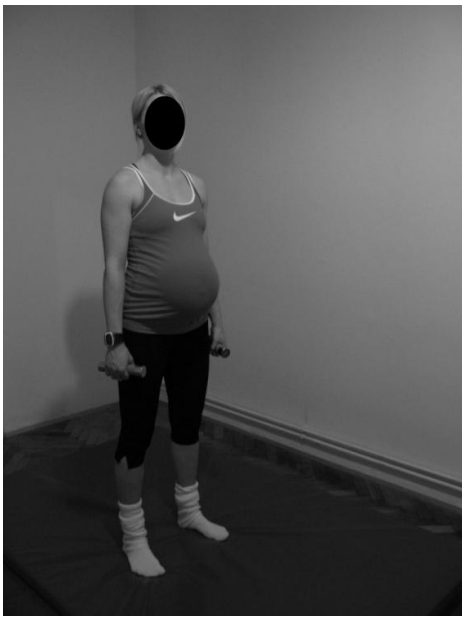
Final position

*Photo: Iva Šklempe Kokić*

Protocol 2

Exercise 1

Starting position



Final position

„Lunge" with free weights

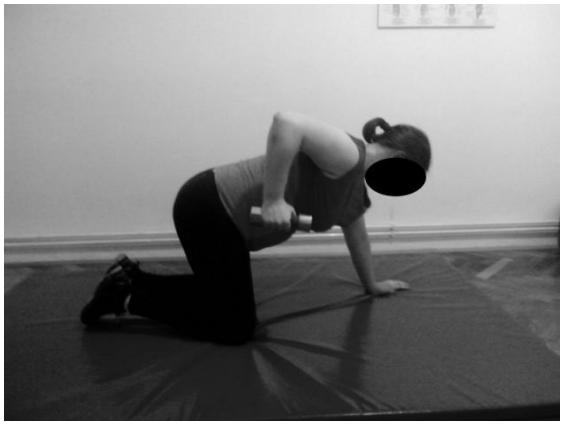
*Photo: Iva Šklempe Kokić*

*Photo: Iva Šklempe Kokić*

Exercise 2

Starting position

Final position



Arm extension with elbow flexion from quadruped position with free weight

*Photo: Iva Šklempe Kokić*

*Photo: Iva Šklempe Kokić*

Exercise 3

Starting position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Leg extension with knees in flexion from quadruped position

Exercise 4

Starting position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Leg abduction from side-lying position

Exercise 5

Starting position

Bilateral arm external rotation with theraband

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 6

Starting position

Back arch exercise („cat and camel")

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Protocol 3

Exercise 1

Starting position

Alternating leg extension with flexed knee from quadruped position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 2

Starting position

Push-up from quadruped position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 3

Starting position

„Side-lunge" with free weights

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 4

Starting position

Leg adduction from side-lying position

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 5

Starting position

„Bridge" (pelvis elevation from supine position)

*Photo: Iva Šklempe Kokić*

Final position

*Photo: Iva Šklempe Kokić*

Exercise 6

Starting position

Bilateral arm abduction

*Photo: Iva Šklempe Kokić*

Final position

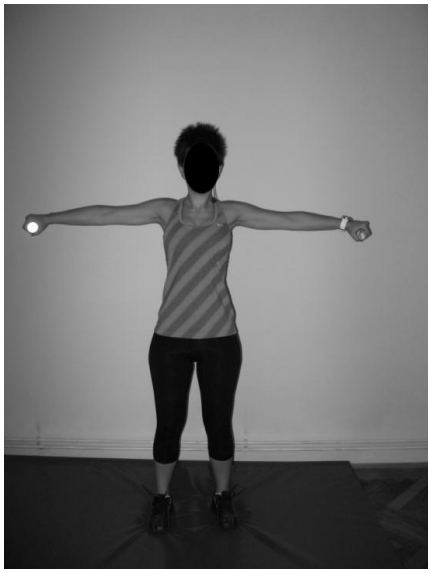


*Photo: Iva Šklempe Kokić*