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Exercise During Pregnancy

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SAMMENDRAG

Friske gravide anbefales å trene regelmessig under svangerskapet for å fortsette å oppnå de samme helsegevinstene som ved trening i ikke-gravid tilstand. Når det gjelder forebygging og behandling av svangerskapsrelaterte plager, har det ikke tidligere vært gjennomført store randomiserte kontrollerte studier for å studere mulig effekt av trening i svangerskapet. Dagens kunnskap er hovedsakelig basert på observasjonsstudier.

TRIP-studien er en to-armet, to-senter, randomisert kontrollert studie og ble gjennomført i perioden 2007-2010. Studien inkluderte 855 friske, gravide kvinner fra Trondheim og Stavanger. Kvinnene ble tilfeldig fordelt i en treningsgruppe og i en kontrollgruppe. Kvinnene i treningsgruppen ble tilbudt et 12-ukers standardisert treningsprogram med ukentlig gruppetrening, ledet av fysioterapeut, og to dager egentrening. Kvinnene i kontrollgruppen fulgte vanlig svangerskapsomsorg. Kvinnene ble testet i svangerskapsuke 18-22 og retestet i svangerskapsuke 32-36.

Målet med denne studien var: **I**) å undersøke om deltagelse i treningsprogrammet kunne redusere forekomsten av svangerskapsdiabetes og gi bedre insulinresistens, **II**) å undersøke om kvinner i treningsgruppen rapporterte mer rygg- og bekkensmerter enn kvinner i kontrollgruppen, **III**) å undersøke om kvinner i treningsgruppen som ble tilbudt et generelt treningsprogram inkludert bekkenbunnstrening, rapporterte mindre inkontinens enn kontrollgruppen og **IV**) å undersøke om energiforbruket, målt med en fysisk aktivitets-monitor, SenseWear[TM] Pro$_2$ Armband, er forskjellig fra energiforbruket målt med indirekte kalorimetri.

Totalt 55 % av kvinnene i treningsgruppen trente tre ganger per uke eller mer på moderat til høy intensitet på slutten av svangerskapet. Til sammenligning trente 10 % i kontrollgruppen tilsvarende ($p<0.001$). **I**) Det var ingen forskjell på gruppene i forekomst av svangerskapsdiabetes eller insulinresistens. **II**) Andelen kvinner med rygg- og bekkensmerter var lik i begge gruppene, men færre kvinner i treningsgruppen var sykmeldt på grunn av rygg- og bekkensmerter. **III**) Forekomsten av urininkontinens var mindre i treningsgruppen, og treningsprogrammet viste seg å ha både forebyggende og behandlende effekt. Det var ingen forskjell på gruppene i andel kvinner som rapporterte analinkontinens. **IV**) SenseWear[TM] Pro$_2$

Armband viste seg å være en god fysisk aktivitetsmonitor for å registrere totalt energiforbruk hos gravide.

Resultater fra TRIP-studien understøtter de generelle anbefalingene om at gravide kvinner bør trene i svangerskapet. En grundig instruksjon i korrekt bekkenbunnstrening og et bekkenbunnstreningsprogram bør inngå i treningsgrupper for gravide kvinner.

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Special thanks to my parents, my best role models, for your endless love and always believing in me. And to my two sisters - the four of you mean a lot to me, and I appreciate your interest and efforts to try to understand what I do for a living.

And finally, I would like to thank my dear husband Børge and our wonderful children, Sigmund and Ingrid, for reminding me about the most important things in life.

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LIST OF PAPERS

I. **Stafne SN**, Salvesen KÅ, Romundstad PR, Eggebø TM, Carlsen SM, Mørkved S. Regular exercise during pregnancy to prevent gestational diabetes: A randomized controlled trial. *Obstet Gynecol* 2012;119:29-36.

II. **Stafne SN**, Salvesen KÅ, Romundstad PR, Stuge B, Mørkved S. Does regular exercise during pregnancy influence lumbopelvic pain? A randomized controlled trial. *Acta Obstet Gynecol Scand* 2012;91:552-559.

III. **Stafne SN**, Salvesen KÅ, Romundstad PR, Torjusen IH, Mørkved S. Does regular exercise including pelvic floor muscle training prevent urinary and anal incontinence during pregnancy? A randomized controlled trial. Accepted for publication in *BJOG*.

IV. Berntsen S, **Stafne SN**, Mørkved S. Physical activity monitor for recording energy expenditure in pregnancy. *Acta Obstet Gynecol Scand* 2011;90:903-7.

ABBREVATIONS

ACOG	American College of Obstetricians and Gynecologists
AI	Anal incontinence
ASLR	Active straight leg raise
BMI	Body mass index
CI	Confidence interval
DRI	Disability rating index
FI	Fecal incontinence
GDM	Gestational diabetes mellitus
HOMA-IR	Homeostasis model assessment–insulin resistance
LBP	Low back pain
LPP	Lumbopelvic pain
mFABQ	Modified fear-avoidance beliefs questionnaire
MoBa study	The Norwegian Mother and Child Cohort Study
OGTT	Oral glucose tolerance test
OR	Odds ratio
PF	Pelvic floor
PFM	Pelvic floor muscle
PFMC	Pelvic floor muscle contraction
PFMT	Pelvic floor muscle training
P4	Posterior pelvic pain provocation test
PGP	Pelvic girdle pain
RCT	Randomized controlled trial
SUI	Stress urinary incontinence
TRIP trial	The Training In Pregnancy trial
T2DM	Type 2 Diabetes Mellitus
UI	Urinary incontinence
UUI	Urgency urinary incontinence
VAS	Visual analogue scale
VPFMC	Voluntary pelvic floor muscle contraction
WHO	World Health Organization

SUMMARY

Healthy pregnant women are encouraged to engage in regular exercise during pregnancy to continue to derive same health benefits as in the non-pregnant state. However, as research on exercise during pregnancy is mainly based on observational studies, there is a lack of large-scale randomized controlled trials to evaluate the role of exercise during pregnancy in the prevention and treatment of pregnancy-related conditions.

The TRIP trial was a two-armed, two-centered randomized controlled trial conducted in 2007-2010. The trial included 855 healthy pregnant women from the areas of Trondheim and Stavanger in Norway. Women were randomized to an intervention or control group. Women in the intervention group were offered a 12-week standardized exercise program with weekly group training led by a physiotherapist and a training program to be performed twice per week at home. Women in the control group received standard antenatal care. Women were enrolled at 18-22 weeks of pregnancy and follow-up was done at 32-36 weeks of pregnancy.

The aims of this trial were: **I)** to assess the efficacy of offering pregnant women a regular exercise program to prevent gestational diabetes and improve insulin resistance, **II)** to assess if women randomized to a regular exercise program were more likely to report lumbopelvic pain than women receiving standard antenatal care, **III)** to assess if pregnant women following a general exercise course including pelvic floor muscle training were less likely to report incontinence in late pregnancy than a group of women receiving standard antenatal care, and **IV)** to assess whether the energy expenditure recorded with the physical activity monitor SenseWear^{TM} Pro$_2$ Armband differs from that recorded with indirect calorimetry.

The adherence to the protocol (exercising three days per week or more at moderate to high intensity) in the intervention group was 55 %. By comparison, 10 % in the control group exercised three days per week at moderate to high intensity at follow-up (p<0.001). **I)** There was no difference between groups in the prevalence of gestational diabetes or level of insulin resistance. **II)** The prevalence of lumbopelvic pain in both groups was similar, however, less women in the intervention group were on sick leave due to lumbopelvic pain. **III)** The intervention group reported less urinary incontinence in late gestation, and the intervention had both a primary and secondary prevention effect. No difference was found in anal

incontinence between groups. **IV)** The physical activity monitor SenseWear^{TM} Pro$_2$ Armband was found to be a valid instrument in pregnant women.

The TRIP trial supports the general recommendations that women should engage in regular exercise during pregnancy and that thorough instructions in pelvic floor muscle training and a pelvic floor muscle training program should be included in general exercise classes for pregnant women.

INTRODUCTION

During the last 20 years there has been increasing interest in the possible benefits of exercise in pregnancy, and pregnant women are encouraged to exercise throughout the pregnancy. However, today's knowledge about the importance of regular exercise in pregnancy is mainly based on results from observational studies. This thesis examines the effect of regular exercise during pregnancy based on a randomized controlled trial (RCT) performed in the period 2007-2010 including 855 pregnant women.

Definitions

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure.[62] Exercise is a subset of physical activity that is planned, structured, and repetitive and has as objective to improve or maintain physical fitness.[62] Physical activity and exercise promote health and longevity, and minimal adherence to current physical activity guidelines is associated with a significant 20-30 % reduction in risk of all-cause mortality.[185] Further reductions in risk are observed at higher volumes of energy expenditure.[185] Disease outcomes and conditions inversely related to regular physical activity include cardiovascular disease, thromboembolic stroke, hypertension, type 2 diabetes mellitus (T2DM), osteoporosis, some form of cancers (colon and breast cancer), anxiety, depression and obesity.[163]

According to the World Health Organization (WHO) physical inactivity has been identified as the fourth leading risk factor for global mortality causing an estimated 3.2 million deaths globally.[338] Among women of reproductive age in the US, physical inactivity declined from 25 % to 23 %, however, obesity increased from 18 % to 25 % from 2001/2003 to 2009.[143]

History

Recognizing the beneficial effects of exercise during pregnancy is not new. In 1901, J. W. Ballantyne, who helped pioneer antenatal care in Edinburgh, designed a card to make sure essential advice during pregnancy was remembered and recorded by his "pre-maternity nurses". This included a tick box regarding exercise and rest.[22] In 1985, the American College of Obstetricians and Gynecologists (ACOG) issued a technical bulletin regarding exercise

during pregnancy.[14] Women were advised to reduce physical activity levels and non-exercising women were to refrain from initiating strenuous exercise programs. The maximum heart rate during pregnancy should not exceed 140 beats per minute and women should not take part in strenuous exercise for more than 15 minutes.[14] This advice was based on concerns that exercise would have negative effect on the mother and fetus secondary due to increased core temperature during embryogenesis, circulating stress hormones, biomechanical stress and increased risk of maternal musculoskeletal injury due to changes in posture and ligamentous laxity, and by shunting the transport of oxygen and nutrients to maternal skeletal muscles rather than to the developing fetus.[83] The recommendations were primarily based on expert opinions because of limited evidence available at that time.

Following these original ACOG guidelines, research over the next 10 years focused on the safety, as well as the potential benefit of physical activity performed during the peripartum period. Results from most studies showed that any effects of physical activity on the maternal-fetal unit are likely to be beneficial. In 1994, ACOG released a new bulletin removing specific limitations and prohibitions regarding exercise during pregnancy.[13] ACOG still recommended that women should avoid exhaustion during exercise. In 2002, ACOG published "Exercise during pregnancy and the postpartum period: ACOG Committee Opinion 267." In this paper, the ACOG Committee recognized that "in the absence of contraindications, pregnant women should be encouraged to engage in regular, moderate intensity physical activity to continue to derive health benefits during their pregnancy as they did prior to their pregnancy".[5]

Physiology

There are profound anatomical, physiological (Figure 1), and biochemical adaptations to pregnancy. Many of these remarkable changes begin soon after fertilization and continue throughout gestation, and most occur in response to physiological stimuli provided by the fetus and placenta.[80] These profound cardiovascular system alterations occur in pregnant women regardless of their physical fitness status.[207] Within five weeks of pregnancy cardiac output increases and reaches 24 % above the non-pregnant level in pregnancy week 24,[153] and almost 50 % above the non-pregnant level in pregnancy week 32.[270] This occurs as a result of increased resting heart rate by 10 beats/min,[295] increased blood volume,[100,153,260,337] and decreased mean arterial pressure.[100,190] At term, the average increase in blood volume is 48

%.[260] The uterine artery volume blood flow and the fraction of cardiac output distributed to the uterine circulation are doubled from gestational week 22 until term.[109] The cardiovascular adaptations are associated with autonomic nervous system changes.[295] The morphologic and functional changes are explained by increased left ventricular mass and increased wall thickness.[153,190] The increased blood volume is mainly due to increased plasma volume resulting in a relative maternal anemia.[337] Additionally, a decrease in systemic vascular resistance is seen due to increased uterine vasculature, uteroplacental circulation, and the decrease in vascular resistance of predominantly the skin and kidney.[109,254,316] Most important maternal cardiovascular adaptations to pregnancy take place in the first eight weeks of pregnancy.[100]
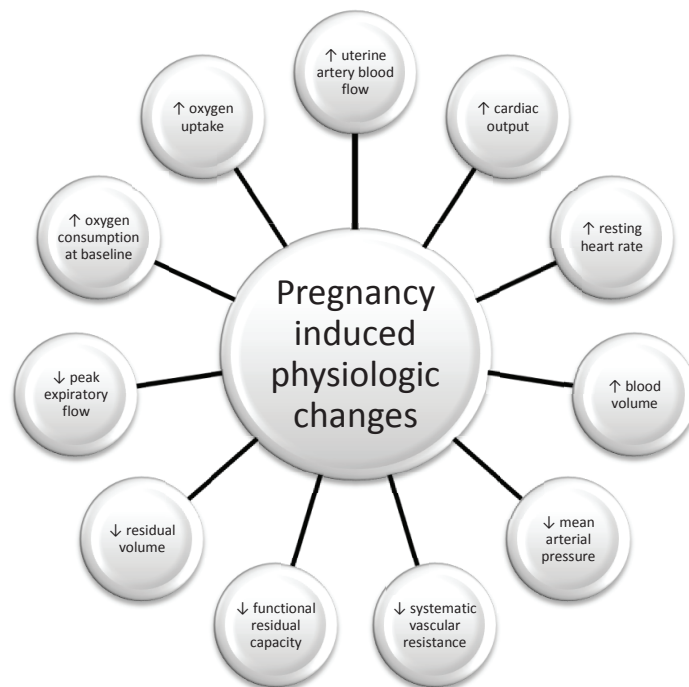
Figure 1. Illustration of pregnancy-related physiologic changes.

The maternal cardiovascular adaptations have several functions and appear to establish a circulatory reserve necessary to provide nutrients and oxygen to both mother and fetus at rest and during moderate physical activity.[80]

The growing uterus causes the diaphragm to rise about 4 cm, the transverse diameter of the thoracic cage increases approximately 2 cm, and the thoracic circumference increases about 6

15

cm.[80] As a consequence of the elevated diaphragm, the functional residual capacity, the residual volume and the peak expiratory flow rates decline progressively as gestation advances.[135] There is increased oxygen uptake and an increase in baseline oxygen consumption.[172] The subjective workload and maximum exercise performance decreases due to increased resting oxygen requirements. Because of the increased work of breathing, caused by pressure of the enlarged uterus on the diaphragm, there is decreased oxygen availability for the performance of aerobic exercise during pregnancy.[18]

The fetal body temperature is about 1.0 °C higher than maternal temperature. To prevent hyperthermia during exercise due to maternal basal metabolic rate and heat production, a steady state of heat production versus dissipation is accomplished by increased conductance of heat from the core to the periphery circulation as well as through evaporative cooling through sweat.[18]

Due to the enlarged uterus, the supine resting position and motionless standing will decrease venous return and cardiac output due to vena cava compression.[74,158] However, exercise in a supine position has not been found to significantly decrease venous return and cardiac output,[158] and does not support guidelines advising against exercises in supine position after 16 weeks of gestation.[5,83] However, when designing exercise programs for pregnant women one should be aware of the possible obstruction of vena cava.

Exercise recommendations for non-pregnant women
In 1995, the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM), issued a public health recommendation about physical activity with the purpose to encourage increased participation in physical activity by a largely sedentary US population.[247] The original recommendations issued that "every US adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week".[247] However, the recommendations were not accepted by some and others have misinterpreted the recommendations. In 2007, the ACSM and the American Heart Association issued an updated version of the 1995 recommendations.[137] The intent was to provide a more comprehensive and explicit public health recommendation for adults based upon available evidence of the health benefits of physical activity.[137]

In the latest recommendations for adults, both aerobic physical activity and strength exercises are recommended to promote and maintain good health and physical independence.[137] Moderate-intensity aerobic physical activity for a minimum of 30 minutes should be performed on five days each week or vigorous-intensity aerobic activity for a minimum of 20 minutes on three days each week. A combination of moderate- and vigorous intensity activity can be performed to meet this recommendation.[137] Activities that maintain or increase muscular strength and endurance should be performed for a minimum of two days each week. It is recommended that 8-10 exercises are performed on two or more nonconsecutive days each week using the major muscle groups.[137] It is further stated that participation in aerobic and muscle-strengthening physical activities above minimum recommended amounts provides additional health benefits and results in higher levels of physical fitness.[137]

Exercise recommendations for pregnant women

From the traditional view that pregnant women should reduce their habitual levels of exercise in pregnancy, there is now agreement that healthy pregnant women should be encouraged to include exercise as part of a healthy lifestyle. Pregnancy is recognized as a unique time for behavior modification and is no longer considered a condition for confinement. It is currently recognized that habits adopted during pregnancy could affect a woman's health for the rest of her life.[18] Current ACOG guidelines for exercise during pregnancy recommend 30 minutes or more of moderate exercise on most if not all days of the week for pregnant women in the absence of medical or obstetric complications.[5] Women with complicated pregnancies have been discouraged from participating in exercise activities for fear of impacting the underlying disorder or maternal or fetal outcome.[83] The recommendations also promote exercise for sedentary women and those with medical or obstetric complications, but only after medical evaluation and clearance (Table 1). Pregnant women should be cautious about participating in contact sports and avoid scuba diving. Due to the anatomical and physical changes during pregnancy, such as weight gain, increased forces across hip- and knee joints and altered levels of hormones, pregnant women are theoretically more predisposed to musculoskeletal injuries. Nevertheless, these possibilities should be considered when designing exercise programs.

Table 1. Absolute contraindications, relative contraindications and warning signs to terminate exercise during pregnancy.

Absolute contraindications to aerobic exercise during pregnancy	Relative contraindications to aerobic exercise during pregnancy	Warning signs to terminate exercise during pregnancy
• Hemodynamically significant heart disease • Restrictive lung disease • Incompetent cervix/cerclage • Multiple gestation at risk for premature labor • Persistent second- or third-trimester bleeding • Placenta previa after 26 weeks of gestation • Premature labor during the current pregnancy • Ruptured membranes • Preeclampsia/pregnancy-induced hypertension	• Severe anemia • Unevaluated maternal cardiac arrhythmia • Chronic bronchitis • Poorly controlled type 1 diabetes • Extreme morbid obesity • Extreme underweight (BMI <12) • History of extremely sedentary lifestyle • Intrauterine growth restriction in current pregnancy • Poorly controlled hypertension • Orthopedic limitations • Poorly controlled seizure disorder • Poorly controlled hyperthyroidism • Heavy smoker	• Vaginal bleeding • Dyspnea prior to exertion • Dizziness • Headache • Chest pain • Muscle weakness • Calf pain or swelling (need to rule out thrombophlebitis) • Preterm labor • Decreased fetal movement • Amniotic fluid leakage

From "ACOG Committee Opinion No. 267: Exercise During Pregnancy and the Postpartum Period".[5]

Pregnant women are advised to participate in moderate intensity exercises.[5] Given the variability in maternal heart rate responses to exercise, target heart rates cannot be used to monitor exercise intensity in pregnancy. However, ratings of perceived exertion have been found to be useful during pregnancy as an alternative to heart rate monitoring of exercise intensity.[253] For moderate exercise, ratings of perceived exertion should be 12-14 (somewhat hard)[18] on a 6-20 scale (Borg scale).[40] Evidence of the efficacy of this approach is that, when exercise is self-paced, most pregnant women will voluntarily reduce their exercise intensity as pregnancy progresses.[206]

Disease prevention

Recently, researchers have begun to consider the role of physical activity in prevention of chronic diseases for both mother and offspring.[255] Over the last 30 years, a substantial body of literature has emerged suggesting that adverse conditions during intrauterine development may have lasting effects on physiology and metabolism of the fetus, resulting in increased disease susceptibility as an adult.[79] The long-term effects of fetal growth on adult health are thought to be the consequences of programming. A programming effect describes a stimulus occurring at a critical sensitive period of early life that has permanent effects on the growth

and metabolism of the organism. These stimuli may lead to alterations in birth size and metabolic changes, such as reduced insulin sensitivity and increased susceptibility to disease later in life.[26] Fetal adaption to an adverse intrauterine environment involves programming of metabolic pathways that might predispose to cardiovascular disease in later life. This adverse environment may change gene expression, leading to physiological phenotypes associated with morbidity and mortality.[27,160] Many of the genes epigenetically influenced by nutrition are also affected by exercise or are involved in metabolic processes that are modulated by exercise.[204] It is therefore reasonable to hypothesize that exercise during pregnancy also could mediate future health outcomes through epigenetic modifications.[96]

Body size at birth is the best available marker for fetal growth and is a rough indicator of the in utero environment. Both high and low birth weight has been found to have adverse associations with later disease. There is a robust relationship between low birth size and all-cause mortality in adulthood, implicating a major impact of intrauterine conditions on health during later life.[160] In a recently published meta-analysis Risnes et al.[264] found that birth weight was inversely associated with adult mortality from all causes and cardiovascular mortality. For cancer mortality there was a linear relationship with birth weight for men, but not for women.

Children with a high birth weight are more likely to become obese.[16,335] In the long run, childhood overweight and obesity is strongly associated with adult obesity, giving more than a fivefold increase in the risk for being overweight in early adulthood.[122,296,311] These results suggest that prevention of obesity should begin as early as possible.

There is now increasing evidence that the effect of the in utero environment on the development of obesity and risk factors for adult disease is U-shaped. Here, the rates of T2DM among persons with low birth weight (<2500 g) and persons with high birth weight (>4500 g) are being almost twice as high compared to persons with normal birth weight.[238,252] Hopkins et al.[151] found that women who exercised regularly from gestational week 20 onwards gave birth to significantly lighter babies than controls (3426 ± 427 vs. 3569 ± 433). Clapp et al.[73] found that women who performed a high volume of exercise in early pregnancy and then cut back their exercise in late pregnancy delivered offspring who were significantly heavier at birth. In contrast, although not statistically significant, the offspring of women who

increased from a low volume of exercise in early pregnancy to a high volume in the second half of pregnancy were on average 100 g lighter than the offspring of a comparative group who maintained a moderate volume of exercise throughout pregnancy. These results suggest that fetoplacental adaptations are dependent on the period of gestation in which exercise training is initiated and maintained, as well as the intensity or volume of the exercise performed.[152]

In utero exposure to hyperglycemia is found to have an intergenerational effect, with women born to diabetic mothers being more predisposed to diabetes in their own pregnancy than women born to non-diabetic mothers.[205] Promoting the health of women of reproductive age before conception and ensuring that women receive the services they need to improve outcomes while they are pregnant is a primary goal of preconception care and the prevention of chronic diseases in future generations.[20] Helping women to maintain a healthy weight before and during pregnancy may be the best hope for controlling the obesity epidemic seen in some countries.

Today's recommendations for exercise in pregnancy are proactive,[5,230] suggesting that virtually all women having a normal pregnancy can benefit from a physical activity program. However, there is a lack of studies examining the potential epigenetic programming effects of exercise during pregnancy.[96]

Pregnancy and level of physical activity
Although exercise is recommended during pregnancy, it is documented that being pregnant is an event that leads to decreased physical activity. Women seem to reduce all levels of physical activity such as household tasks, care giving and active living, but the largest reduction is seen in participation in sports and exercise.[105] In the Norwegian Mother and Child Cohort Study (MoBa study), including 34,508 pregnancies in Norway, the proportion of regular exercise defined as exercising three times per week or more, was 46 % before pregnancy and declined to 28 % and 20 % by gestational weeks 17 and 30, respectively.[244] Multiple pregnancy, pelvic girdle pain, nausea, musculo-skeletal pain, uterine contractions and sick-leave were factors inversely associated with regular exercise in the MoBa study.[244] Sociodemographic characteristics positively associated with exercising during pregnancy are

high education, low body mass index (BMI), primiparity and being a cohabitant.[60,105,149,244] Regular exercise prior to pregnancy is strongly associated with regular exercise during pregnancy, and women with high levels of pre-pregnancy physical activity are more likely to exercise during pregnancy.[60,105,149,244]

Beliefs and behavior

In a qualitative study of 19 Australian pregnant women, motivating factors that facilitated women's engagement in physical activity included access to exercise classes, using a personal trainer, receiving advice from health professionals, being with other pregnant women, wanting to stay in shape with a controlled weight gain, and receiving reassurance that their pregnancy was progressing satisfactorily. In addition control of physiological events such as constipation and incontinence, and the baby's well-being were motivating factors.[72] The same study identified barriers to be physical active such as feeling unwell or tired, physical discomforts, such as backache and sore knees, pressure from the uterus, breathlessness and decreased motivation and lack of time because of work and having previous children.[72]

Most women report that they obtain the information about exercise in pregnancy from books, the web, parental magazines, publications issued free at antenatal clinics, and health care professionals.[72,75] In a study by Clarke et al.,[75] only 18 % reported receiving advice directly from the health professionals involved in their antenatal care. Women reported that the information received was often unclear, confusing, inconsistent or conflicting.[72,75] On the other hand, women who are informed about the benefits and risks of physical activity and exercise techniques, have more favorable attitudes towards physical activity.[60]

Following the reduction in activity during pregnancy, the activity levels are found to be 1.4 hours per week below pre-pregnancy levels at six months postpartum. This is associated with increased body weight retention during the first six months of the postpartum period.[250] Several factors related to the time available for exercise predicted the likelihood of insufficient activity, including employment, number of children at home, and child care barriers.[250] Women who temporary halt exercise during pregnancy, tend not to resume their exercise habits postpartum to the same extent as women who continue exercising during pregnancy.[103]

Among pregnant women the importance of rest and relaxation are rated significantly higher than having an active lifestyle and exercising regularly.[75] Although most mothers understand the benefits of physical activity in pregnancy, that does not seem to translate in to practice. The pregnancy and the postnatal periods are prime opportunities for raising women's awareness of health strategies to enable them to nurture their optimal well-being.[72] There is considerable scope for improving the quantity and quality of advice in this area.[75] Antepartum care providers should increase women's awareness of the benefits of activity in pregnancy, provide reassurance about safety concerns, and present options to women that can guide their incorporation of recommended activity levels into their daily lives.[72]

Validation of physical activity

Physical activity is characterized by its intensity, duration, frequency and mode of activity.[218] Ideally, all these aspects should be recorded during physical activity measurements. However, in most studies addressing effects of physical activity in pregnancy, the validity of activity reports is open to discussion.

Data collection of physical activity most frequently involves self-reporting (subjective) measures, such as questionnaires, diaries, logs, surveys and interviews. The benefits of self-reporting measures are their practicality, low cost, low participant burden and general acceptance.[94] However, the self-reporting methods have limitations such as recall and response bias and the inability to capture the absolute level of physical activity.[259] Direct measures are believed to offer more precise estimates of energy expenditure and remove many of the issues of recall and response bias. There are several methods for assessing direct physical activity such as calorimetry (i.e., doubly labelled water, indirect, direct), physiological markers (i.e., cardiorespiratory fitness, biomarkers), motion sensors and monitors (i.e., accelerometers, pedometers, heart rate monitors).[259] However, there is no single "golden standard" for measuring physical activity or assessing its validity.[94]

A systematic review included 148 studies on non-pregnant adults and reported the correlation between self-reports and direct measurements of physical activity. However, there was no clear trend in the degree of correlation between self-reported and directly measured physical activity, regardless of the direct method used. The correlation was generally low-to-moderate

with a mean of 0.37, ranging from -0.71 to 0.96.[259] The correlation was higher in studies reporting results for males (r=0.47 on average) versus studies reporting results for females (r=0.36 on average), but with very similar ranges. In general, self-reported physical activity estimates were higher than those measured by directly methods.[259] In overweight or obese individuals, self-reported physical activity was overestimated in all cases.[259] Among 153 adults aged 35-65 years, Ferrari et al.[107] found that the accuracy of physical activity questionnaire measurements was higher for men than for women, for younger individuals and for those with lower BMI.

One challenge in assessing physical activity is that women as a group spend more time on household and family activities than men. In surveys that did not include these activities, women tend to underestimate their activity level.[7] In a review by Prince et al.[259] some results suggest that patterns in the agreement between self-reports and direct measurements of physical activity may exist, but they are likely to differ depending on the direct methods used for comparison and gender. Differences between the self-report and direct measurements increase with the higher category levels of intensity.[259] The fact that intensity is the least valid component assessed by self-reporting is supported by Sallis and Saelens who found that young people and adults overestimate their physical activity, particularly vigorous intensity activities.[276]

Despite the advantages of using direct methods, these types of measurements are often expensive and time consuming resulting in difficulties in applying them to large populations. The direct methods also require specialized training and the physical proximity of the participant for data collection.

Since resting metabolic rate and absolute energy cost during physical activity are increased in pregnant women,[271,322] activity monitors must be validated in this specific population.[330] To be able to give recommendations based on evidence, valid measurement tools are important.[68] One possible bias is that the activity monitors used have not been validated in the pregnant population.

Validation studies quantifying the impact of measurement errors on physical activity estimates are essential to evaluate the impact of physical inactivity on health.[107] The validity

of activity monitors needs to be carefully examined in the actual research population.[330] To my knowledge, few have evaluated activity monitors for use during pregnancy.[68] Valid and reliable measurements of energy expenditure and physical activity are critical to understand the influence of physical activity on pregnancy outcomes.[68]

In this thesis I will look into the influence of exercise during pregnancy on gestational diabetes and the two most common pregnancy-related muscelosceletal disorders; lumbopelvic pain and incontinence.

Gestational diabetes

Definition

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with onset or first recognition during pregnancy[210] and is usually diagnosed by an oral glucose tolerance test (OGTT), however, the OGTT procedure and the diagnostic criteria used vary.[70]

Prevalence of GDM

The prevalence of GDM has been reported up to 14 %.[159] It has increased worldwide, however, there is variation in diagnostic criteria, ethnicity and the population studied.[159,343] A prevalence of 5.6 % was found (unpublished data) in a cohort of a Scandinavian population in Oslo. This was in the "Stork" study conducted in 2002-2008 (N=1,032). In the "Stork Groruddalen" research program, conducted at the same time that included an urban Norwegian population (N=759), a prevalence of 13 % was found in gestational week 28 ± 2.[224] In 2009, 1.3 % of all pregnancies in Norway were registered as having GDM in the Medical Birth Registry of Norway.[307] However, pregnant Norwegian women are not screened for GDM on a regular basis, and only women with identified risk factors are offered OGTT. Thus, the prevalence is probably underreported in the Medical Birth Registry of Norway, and the true prevalence is unknown.

Risk factors for GDM

The risk of diabetes in pregnancy reflects the underlying frequency of T2DM for a given population.[168] Identified risk factors for GDM are obesity (BMI>30) diagnosed before pregnancy,[314] ethnicity,[168] polycystic ovarian syndrome,[315] essential hypertension,

hypertension in pregnancy,[145] family history of diabetes in first-degree relatives and a history of GDM in previous pregnancy.[1] In a population-based cohort study of 96,801 nulliparous pregnancies in the US, the proportion of women who developed GDM, consistently increased with increasing BMI. Both pre-pregnancy obesity and overweight were found to increase the risk of GDM.[21]

Metabolic changes during pregnancy

Pregnancy has been characterized as a diabetogenic event due to hormones with diabetogenic effects (estrogen, prolactin, human chorionic somatomammotropin, HPL, cortisol, and progesterone). The diabetogenic effects of these hormones lead to insulin resistance and increased insulin requirements.[17] Insulin resistance is a physiological condition in which the natural hormone insulin becomes less effective in lowering blood sugars. The metabolic changes are in response to the increased demands of the rapidly growing fetus and placenta. By the third trimester, the maternal basal metabolic rate is increased by 10-20 % compared with that of the non-pregnant state.[80] Among the nutrients crossing the placenta, glucose is quantitatively the most important, and is the primary energy source for feto-placental tissues. The glucose supply to the fetus is via passive glucose diffusion and therefore it is concentration dependent.[142]

A normal pregnancy is characterized by mild fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia. This response is consistent with a pregnancy-induced state of peripheral insulin resistance, the purpose of which is likely to ensure a sustained postprandial supply of glucose to the fetus. Insulin sensitivity in late normal pregnancy is 50-70 % lower than that of non-pregnant women.[49] The mechanisms responsible for insulin resistance are not completely understood.[80]

GDM and associated short- and long-term risk factors

GDM is a risk factor for pregnancy complications,[165,283] and is associated with short- and long-term morbidity in both the mother and the offspring.[39,81,147,166,167] It is unclear if the complications are due to elevated glucose levels per se or by unidentified factors. In the case of maternal hyperglycemia and placental normal function, there will be increased placental

transfer of glucose, fetal hyperglycemia develops and hyperinsulinism secondary to this alteration. As insulin is one of the main growth factors during fetal life, this hyperinsulinemia leads to macrosomia and to the complications secondary to the delivery of a large baby. Even minor degrees of hyperglycemia are associated with adverse outcomes. In the HAPO study, including 23,316 pregnant women who underwent a 75 g OGTT at 24-32 weeks of gestation, a strong continuous association was found between maternal glucose tolerance and a number of different adverse pregnancy outcome events even in the sub-diabetes range. There were positive associations between increasing levels of fasting, 1-hour, and 2-hour plasma glucose obtained by OGTT and birth weight above the 90th percentile, preterm delivery, shoulder dystocia, birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia.[211]

In the long term GDM is associated with risk factors for cardiovascular disease,[180] and a higher risk of developing T2DM during the next 5-10 years for the mother.[167] A meta-analysis found that women with GDM have at least a seven-fold increased risk of developing T2DM compared with those who had a normoglycaemic pregnancy (RR 7.43, 95 % CI 4.79-11.51).[29] And women developing GDM have a higher risk of the recurrence of GDM in the next pregnancy.[166] Children born in GDM pregnancies have a higher risk of childhood obesity,[147] metabolic syndrome[39] and T2DM as adolescents.[81] In addition, children born in GDM pregnancies have a higher risk of developing GDM in their own pregnancy compared to children born to non-diabetic mothers.[205]

Many of the risk factors for GDM and T2DM are the same (a family history of diabetes, raised BMI, increased age, and Asian and black origin) suggesting that the two disorders might have overlapping causes.[29]

Exercise and glucose homeostasis

In the non-pregnant state, physical activity improves glucose homeostasis through a direct or indirect impact on insulin sensitivity.[15,41,88] Both aerobic and resistance training improve insulin sensitivity as shown by a reduction in the insulin response to a glucose load, and an improvement in peripheral insulin sensitivity. Muscle contractions stimulate glucose uptake in the complete absence of insulin. The effects of muscle contraction and insulin are additive, and the contraction and insulin stimulate glucose transport by separate pathways.[140] However,

exercise must be undertaken regularly to have beneficial effects.[77,140] Both in prevention and treatment of T2DM, exercise plays an important role.[77] A meta-analysis found that all types of exercise reduced the HbA_{1c} levels in T2DM to a similar magnitude as those exerted by long-term dietary, drug and insulin therapy.[291] Therefore, regular sustained aerobic exercise in pregnant women may have the same effect and counteract the normal state of insulin resistance in late gestation. In the ACOG's latest version from 2002 it is suggested that exercise has a possible role in the prevention and management of GDM.[5]

Among non-pregnant women with T2DM, the intensity and duration of physical activity seem to be the most important factors that influence energy expenditure. However, there are conflicting results about whether the intensity or the volume of exercise is the most important determinant for the improvement of insulin action.[139] Physical activity causes increased glucose uptake into active muscles balanced by hepatic glucose production, with a greater reliance on carbohydrate to fuel muscular activity as intensity increases. An increase in muscle mass from resistance training may contribute to blood glucose uptake from a mass effect.[63] Combined strength and aerobic training is found to be superior to either type of exercise alone.[291] In addition, the supervision of exercise sessions by qualified exercise trainers is found to be important for the best effect on blood glucose, and there should be no more than two consecutive days between bouts of aerobic activity.[77] For those with T2DM, strength and aerobic training are recommended as well as initial instruction and periodic supervision by a qualified exercise trainer.[77]

The role of exercise in prevention of GDM
The effect of exercise on the development of gestational diabetes has been sparsely studied, and the study results are conflicting.[23,59,151,313] In a systematic search on PubMed no previous RCT's addressing the effect of physical activity in prevention of GDM in a general population of pregnant women were found (Table 2). Two recent trials assessed maternal glucose level and insulin sensitivity respectively with conflicting results. However, the study populations were small, only 84 and 83 subjects.[23,151] Results from one meta-analysis demonstrate that greater total physical activity before or during early pregnancy is associated with a lower risk of GDM, with the magnitude of the association being stronger for pre-pregnancy physical activity.[313] There is a lack of large RCTs that have a sufficient methodological quality to

assess the effects of adequate regular exercise in pregnancy on glucose homeostasis.[220] Two protocols for assessing exercise in the prevention of GDM in women at risk are published.[69,243] A protocol for a Cochrane review on exercise for pregnant women in the prevention of GDM has recently been published.[127]

The prevalence of GDM doubled from 1994 to 2002 in a multiethnic population in Colorado, US.[82] The trend toward older maternal age, the epidemic of obesity and diabetes, and the decrease in physical activity and the adoption of modern lifestyles in developing countries may all contribute to an increase in the prevalence of GDM.[106] Identifying ways that might help prevent GDM is a matter of urgent public health importance.

Table 2. Randomized controlled trials assessing the effect of exercise during pregnancy on maternal glucose level, insulin resistance and prevalence of gestational diabetes.

Author	Subjects	Design / Intervention	Outcome measures	Results (IG vs. CG)	Comments
Barakat et al. (2011)[23]	N=100 Caucasian Nulli-/multipara Included between 6-9 wk' of pregnancy	2 arm RCT 1. Control. 2. Intervention: 35-45 minutes physical conditioning program 3x/week (land x2 and aquatic activities x1). Light to moderate intensity, less than 70 % of age-predicted maximum heart rate (monitored with heart rate monitor). Intervention period from 6-9 wk' until 38-39 wk' of pregnancy.	1 h non-fasting 50 g maternal glucose screen (MGS) and cases of GDM in 24-28 wk' of pregnancy. Women with 1 h glucose ≥140 mg/dl were referred for a 100 g fasting 3 h OGTT Maternal weight	50 g MGS (mg/dl): 104 ± 20 vs. 127 ± 30 ($p<0.001$) GDM-cases 0/40 vs. 3/43 ($p>0.05$) Weight gain: 13 ± 3 vs. 14 ± 3 ($p>0.05$) No differences in pregnancy outcomes	17 were lost to follow-up, 83 subjects were analyzed 85 % adherence to the exercise protocol No measurement of glucose level at study enrolment All exercise sessions were in classes No control of level of exercise in CG
Hopkins et al. (2010)[151]	N=98 Nullipara Included before 20 wk' of pregnancy	2 arm RCT 1. Control: continue normal daily activities. 2. Intervention: home-based aerobic exercise program using stationary cycling. Individually prescribed to a maximum of 5x/week of 40 minutes. Moderate exercise intensity of 65 % of predicted VO_{2max}. Intervention period: 19-36 wk' of pregnancy. Compliance was assessed by self-reported exercise diaries and downloadable heart rate monitors, and reported as the percentage of prescribed weekly exercise duration complited.	Insulin sensitivity index measured at 19 and 34-36 wk' of pregnancy. After an overnight fast, participants underwent a 180 minutes intravenous glucose tolerance test [dextrose (300 mg/kg body weight as a 25 % solution in normal saline) was infused over 60 seconds] Birth weight	Insulin resistance (10^{-4}/min μU/ml) (mean and 95 % CI): 3.6 (3.0-4.4) vs. 3.7 (3.2-4.4) (p=0.95) Birth weight adjusted for gender and gestational age reported as an SD score were lower in IG No differences in maternal weight and BMI at follow-up	14 lost to follow-up, 84 subjects were analyzed Baseline assessments of insulin sensitivity were performed Overall compliance during the intervention period was 75±17 % No control of level of exercise in CG

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PubMed search term: ("Diabetes, Gestational"[Mesh] OR "Pregnancy in Diabetics"[Mesh] OR "Pregnancy"[Mesh] OR "gestational diabetes"[tiab]) OR (("Pregnancy"[Mesh] OR "Pregnancy Complications"[Mesh:NoExp] OR maternal[tiab] OR pregnan*[tiab] OR gestational[tiab]) **AND** ("Glucose Metabolism Disorders"[Mesh] OR Blood glucose/metabolism[mesh] OR insulin[mesh] OR "insulin sensitivity"[tiab] OR diabet*[tiab])) **AND**

("Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Physical Fitness"[Mesh] OR "Physical Exertion"[Mesh] OR "Motor Activity"[Mesh] OR "Sports"[Mesh] OR exercis*[tiab] OR training[tiab] OR ("physical activity"[tiab] NOT medline[sb]) AND (clinical trial[pt] OR random*[tiab] OR trial[tiab] OR group[tiab] OR groups[tiab] OR systematic[sb]) NOT ((Animals[mesh] NOT Humans[mesh]) OR Case reports[pt])

BMI denotes Body Mass Index, CG control group, GDM gestational diabetes, IG intervention group, OGTT oral glucose tolerance test.

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Lumbopelvic pain

History

Historical evidence shows that pelvic girdle pain (PGP) in pregnancy was already known and recognized many centuries ago. Symphysis pubis dysfunction was mentioned by Hippocrates (ca. 400 BC) in his theory of "disjunction pelvica".[28] According to Hippocrates, the widening of the symphysis pubis only occurred during the first parturition, and then remained permanent and sufficient for later childbirths. The first to give a description of the clinical aspects of pelvic insufficiency in Norway was Skajaa, who in 1929 observed symptoms of pelvic insufficiency in 31 (16 %) of 185 patients from his private consultations.[115]

Definition

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[157] Pain is an individual and subjective experience that depends on a variety of biological, psychological and social factors.[78] Low back pain (LBP) is usually defined as pain between the 12th rib and the gluteal fold, while PGP is defined as pain experienced between the posterior iliac crest and the gluteal fold, particularly in the vicinity of the sacroiliac joints. The pain may radiate in the posterior thigh and can also occur in conjunction with/or separately in the symphysis.[326] Although similar and overlapping mechanisms may be involved between PGP and LBP, some researchers argue that a distinction should be made.[326] A clinical examination including pain provocation tests and/or tests of functional disturbances must be performed to distinguish between LBP and PGP,[326] but the criteria are unclear. In this thesis the pain is referred to as lumbopelvic pain (LPP), no specific distinction is made between LBP and PGP except when this distinction is made in the references.

Prevalence of LPP

LPP during pregnancy is a common disorder. A review has reported an average prevalence of 45 % with variations from 4-90 %.[342] The variation is probably due to differences in study design and diagnostic procedures.[326] Most of the literature use self-reports of LPP. It has been

shown that self-reporting generally reports 20 % higher prevalence than medical records, indicating that women in questionnaires report mild pain that normally would not come to the attention of the medical profession.[342] In the MoBa study including 75,939 pregnancies, 58 % reported pain in one or more pelvic locations during pregnancy week 30, with 13 % reporting severe pain in one or more pelvic locations.[34]

It has been stated that LPP is more common in the Scandinavian countries than the rest of the world.[193] However, studies show that LPP is common in many countries,[35,67,76,98,216,219,221,312,329] irrespective of the socio-economic status of the countries.[35] The majority of studies on LPP have been performed in the Scandinavian countries. One explanation for the assumed higher prevalence in Scandinavia may be that outside of Scandinavia pregnancy-related PGP is regarded as a normal pregnancy complaint rather than a syndrome.[28]

Risk factors for LPP

Identified risk factors with strong evidence are reported to be strenuous work, previous low back pain, previous LPP during or after pregnancy, and previous trauma to the pelvis.[326,342]

It has been suggested that the hormone relaxin, which is known to remodel pelvic connective tissue in several mammalian species during pregnancy, plays an important role in the development of LPP. However, study results on the levels of relaxin and LPP are conflicting,[10,178] and further research is needed to assess the possible role of relaxin and other pregnancy-related hormones in the development of LPP. Bjelland et al.[33] found an inverse association between age at menarche and pelvic girdle syndrome (pain in all three pelvic joints) in the MoBa study, suggesting an association between hormonal factors and PGP.

In the same cohort, Bjelland et al.[34] found a positive relationship between parity and pain in all three pelvic locations, with a stronger association for severe pain. Other factors associated were previous LBP, emotional distress, BMI ≥ 30 kg/m^2, physically demanding work, daily smoking, low maternal age and lower educational level.[34] In another cohort (N=891), high BMI, low educational level, parity, previous LPP, a history of hypermobility and amenorrhea were factors influencing the risk of developing LPP.[216] Albert et al.[9] divided pregnant women

with PGP into five subgroups regarding pain location. They found different risk factors for the different subgroups, but common risk factors for all subgroups were a history of previous LBP, trauma of the back or pelvis, multiparity, high levels of stress, and job dissatisfaction. In a cross-sectional study including 283 pregnant women, Robinson et al.[268] found that results from the Posterior Pelvic Pain Provocation test (P4) and Active Straight Leg Raise (ASLR) contributed independently to decreased physical ability in pregnancy week 30.

LPP is considered to be a normal condition of pregnancy expected to spontaneously disappear after delivery.[233] However, some women do not recover after birth. Albert et al.[9] found a rapid decline in the number of diseased in the first three months after delivery, but after three months recovery was slow. Women classified with pelvic girdle syndrome had the worst prognosis, and those with symphysolysis had the best.[9] The average prevalence of LPP postpartum is 25 %, with variations from 0.3 % to 67 %, and approximately 5 % report serious LPP.[342] High age, early onset of symptoms in the pregnancy, severe pain at early gestation and low rate of weight retention postpartum are associated with persistent pain two years after pregnancy.[312] High pain intensity during pregnancy indicated a poor prognosis after pregnancy.[349] Women who have not recovered, have reduced quality of life compared to the general population.[298,299] It has been suggested that poor coping strategies may be involved in the development of long-term pelvic pain postpartum.[133] Olsson et al.[242] found that pain catastrophizing and physical ability mid-pregnancy are predictors of postpartum LPP. Vøllestad and Stuge found that the ASLR test and belief in improvement were strong and independent predictors of clinical significance in women with PGP postpartum.[328]

Influence of LPP on daily life
LPP interferes with ordinary daily activities[249] and reduces the quality of life.[241] Considerable difficulties with activities such as housekeeping, walking, working and sexual life have been reported.[134,214] Although the reported prevalence of LPP is more than 50 % in most studies,[34,67,123,216,221,241,268,312,329] the majority of women are mild to moderately affected as shown by the average scores in pain and disability.[67,266]

The median Disability Rating Index (DRI; an instrument for assessment of physical disability with scores in the range of 0-100) in a group of healthy women aged 30-39 years was <1.[275]

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Olsson et al.[240] found a median DRI score for pregnant women without LPP to be 10 and 27 in women with LPP in mid-pregnancy. In late pregnancy the corresponding numbers were 24 versus 54 in women without and with LPP,[241] indicating more limited physical activity with advancing gestation. Higher DRI scores in women with LPP are also found in other studies.[123,177,266] This suggests that pregnancy and LPP has an additive effect. Higher DRI in pregnant women without LPP than non-pregnant women underscores that even pregnancy in itself constitutes physical disability.

Evidently, there is a wide range in the expression of the symptoms of LPP during pregnancy, and women are affected to various degrees.[214] Some women experience pain in a very early stage of pregnancy, while others only experience pain in the final stage of pregnancy.[266] In addition, some women have more restricted activities due to pain compared with other women. This suggests that other factors than hormonal and/or physiological changes might influence the prevalence of LPP during pregnancy. One recent study found that women with LPP in mid-pregnancy showed more pain catastrophizing and fear-avoidance beliefs than women without LPP.[240] Of women with LPP during pregnancy, around 45 % have mild symptoms only; 25 % have severe pain; and 8 % are severely disabled.[342] In a retrospective cohort study from Norway in 1998-99, 7 % of all women reported the use of crutches during pregnancy due to PGP.[267] The localization and the nature of the pain vary. In pain research it is well known that there are large individual variations in pain ratings, even in patients with the same condition.[231] The proportion of women with severe LPP in need of treatment has been shown to be close to 25 %.[342]

Etiology, anatomy and function
The etiology and pathophysiology of LPP is unknown. During pregnancy there are considerable changes in biomechanics and posture, when the center of gravity is moved anteriorly. Progressive lordosis is a characteristic feature of normal pregnancy. Compensating for the anterior position of the enlarging uterus, the lordosis shifts the center of gravity back over the lower extremities. This curvature and reinforcement of the lumbar vertebrae has evolved in humans to permit bipedal posture and locomotion despite up to a 31 % increase in the maternal abdominal mass by term.[336] The anatomy and function of the pelvis is due to a combination of specific anatomic features (form closure) and the compression generated by

muscles and ligament (force closure).[327] This system prevents shear forces and is called the self-bracing mechanism[290] (Figure 2). In 1992, Panjabi presented a model of the spinal system consisting of the passive, the active and the neural subsystems.[246] The vertebrae, discs, and ligaments constitute the passive subsystem. All muscles and tendons surrounding the spinal column that can apply forces to the spinal column constitute the active subsystem. The nerves and central nervous system comprise the neural subsystem, which determines the requirements for spinal stability by monitoring the various transducer signals, and directs the active subsystem to provide the needed stability.[246] Later Lee and Vleeming further developed this into a more integrated model of function of the lumbopelvic region. They used the terms form closure (passive subsystem), force closure (active subsystem), motor control (neural subsystem) and added emotion/awareness as a fourth component.[183,184] The importance of the pelvic floor muscles (PFM) to increase the stiffness of the pelvic ring has been illustrated in a biomechanical study.[256] During pregnancy the passive stiffness of the spine and the pelvis is likely reduced due to increased ligament laxity. In addition, the ability of some of the muscles to produce stabilizing force, particularly the abdominal muscles, may be compromised.[97] When the muscular capacity and the tension of the ligaments are inadequate, decreased compression across the sacroiliac joint will occur, insufficient stability will follow, and optimal load transfer between the back and legs will be comprised.[257]
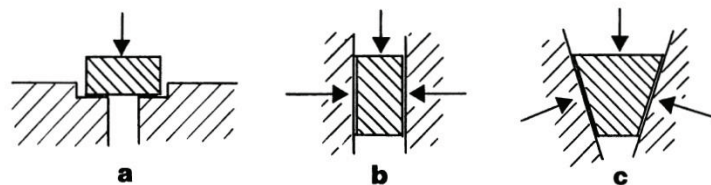
Figure 2. Form closure (a) and force closure (b) lead to a self-bracing mechanism (c). Printed with permission from C.J. Snijders©.

New debates have arisen in the literature concerning the role of muscle function in LBP in the general population, and there is evidence of an association between reduced muscle function and the development of LPP in pregnant women.[97] A pilot study suggests that pregnant women with gluteus medius weakness are 6 to 8 times more likely to have LBP than those without weakness.[30] Gutke et al.[124] found that women with LPP had muscle dysfunction in terms of lower levels of trunk muscle endurance and hip extension muscle strength as well as slower preferred gait speed compared with the women without LPP, both mid-pregnancy and

postpartum. Women with PGP had lower levels of back flexor endurance compared to women without LPP.[124] In addition, Gutke et al.[125] found that low endurance of back flexors, older age, combined pain in early pregnancy and work dissatisfaction were predictors of having persistent PGP or LPP three months postpartum. Sihvonen et al.[289] found a relationship between LBP and muscle activity. They reported that the lower the back muscles activity during the first trimester of pregnancy, the greater the chances to experience LBP and disability throughout the pregnancy. De Groot et al.[84] showed that pregnant women with LPP used more muscle activity, produced less force and scored higher on the ASLR compared to controls.

The combined effect of the muscle dysfunction identified in these studies and the hormone-induced increased ligament and joint capsule laxity in pregnancy, may increase the risk of insufficient force closure of the pelvis giving continuous strain on the pelvic ligaments and resulting in pain.[257] Results from these studies strengthen the hypothesis that there is an association between muscle dysfunction and women who develop or have persistent LPP. However, it is not known if identifying women at risk in early pregnancy and offering them an intervention of strengthening adequate muscles, will prevent LPP.

Sick leave

In Norway, 59 % of pregnant women are on sick leave at least once during pregnancy with an average of 21.5 days off work.[223] Comparable numbers for other countries may differ with type of social welfare system.[304] LPP accounts for most of the sick leave among pregnant women in Scandinavian countries,[121,223,305,350] causing a high impact in terms of loss of production and socio-economic costs. It has been demonstrated that women with postpartum PGP may have difficulties in returning to work.[133]

Exercise

Despite that women are encouraged to exercise during pregnancy, being pregnant seems to be an event that leads to reduced physical activity[105,244] and women experiencing LPP are less likely to exercise regularly.[244] A recent cross-sectional study showed that sedentary coping strategies were more frequent in women with LPP.[67] This is supported by another study which

found that rest and relaxation were perceived as being significantly more important during pregnancy than regular exercise.[75]

In the short term, resting and guarding may temporarily relieve pain. However, in the long run inactivity leads to deconditioning and weakening of muscles, which in turn predisposes a person to loss of function and pain. In the non-pregnant population there is general agreement that the best strategy in the treatment of chronic LBP seems to be encourage physical activity and exercise.[8] A cross-cultural myth still suggests that pregnant women should be inactive and rest in order to protect the safety of the fetus.[72] European guidelines[326] and a Cochrane review[249] clearly indicate the importance of both exercise and relaxation for pregnant women to enhance overall health and prevent pain during pregnancy.

Besides being physically active maintain or improve fitness,[208] observational studies have demonstrated that physical activity before pregnancy may reduce the risk of developing LPP.[89,182,215] Also there is a reduced need for sick leave due to LPP.[350] The explanation may be that women in good physical condition will probably handle the hormonal and biomechanical changes during pregnancy better. Another explanation may be that previous physical activity clearly is a determinant of actual physical status.[215]

The influence of exercise on LPP

There is a lack of RCT's assessing the effects of physical activity to prevent or treat LPP in pregnant women. In a systematic literature search on PubMed (Table 3) only one RCT was found that assessed the preventive effect of exercise on LPP. The trial, including 301 nulliparous women, assessed the effect of a 12-week intervention program with main focus on pelvic floor muscle exercises. At gestational week 36 the authors found a prevalence of self-reported LPP of 44 % in the intervention group versus 56 % in the control group (p = 0.03). No difference was seen in sick leave due to LPP.[228] Ten trials have assessed the role played by physical exercise on treatment of LPP. In general, seven out of ten trials found a positive effect from the intervention in the meaning of reduced pain intensity and/or improved functional ability compared to the control group.[114,120,161,164,170,287,302] However, the trials are not comparable due to different interventions, length of intervention, intensity of intervention

and outcome measure. Four trials found reduced need for sick leave in the intervention group.[120,164,234,350]

There is a lack of RCT's assessing the effects of physical activity for pregnant women. Thus, both prevention and possible adverse effects on LPP and general disability as well as the effects on work related outcomes are sparsely studied.[249]

Table 3. Randomized controlled trials assessing the effect of exercise during pregnancy to prevent or treat lumbopelvic pain.

Author	Subjects	Design / Intervention	Outcome measures	Results (IG vs. CG)	Comments
Kluge et al. (2011)[170]	N=50 LBP (pain from Th12 to the gluteal fold) with onset during pregnancy Nulli-/multipara Included between 16-24 wk' of pregnancy	2 arm RCT 1. Control: written and verbal information on basic back care and posture during pregnancy. 2. Intervention: written and verbal information on basic back care and posture during pregnancy, and a written exercise program. The exercise program consisted of specific stabilizing exercises and PFMT performed daily. Group training sessions were held every second week. 10 wk' intervention period.	Pain intensity (Numerical rating scale – Brief Pain Inventory, 6 item questionnaire, score range 0-60) Functional ability (Likert-modified Roland-Morris Disability Questionnaire)	After a 10 wk' intervention period Pain intensity: 19 (0-40) vs. 33 (5-50) (p<0.01) Significantly reduced pain intensity from baseline to follow-up in IG, not in CG Functional ability: 40 (0-135) vs. 77 (4-140) (p=0.03)	4 were lost to follow-up Power calculation suggested 38 subjects in each group, the trial were underpowered Median number of home exercises performed were 37 (range 3-74) Median number of exercise classes attended were 3 (range 0-5)
Kashanian et al. (2009)[161]	N=30 Nullipara Non-exercises Included at 16 wk' of pregnancy	2 arm RCT 1. Control: routine prenatal care. 2. Intervention: 1 h initial training session in which 7 main exercises together with preparation and relaxation exercises were taught. Women were encouraged to perform aerobic and strength exercises for 30 minutes 3x/week. 8 wk' intervention period.	Functional ability (Roland-Morris questionnaire) Lordosis	After an 8 wk' intervention period Functional ability: 26 ± 2 vs. 32 ± 5 (p=0.001) Lordosis angle: 42 ± 7 vs. 42 ± 6 (p=0.91)	No data on adherence to the exercise protocol Women with pelvic pain were excluded
Morkved et al. (2007)[228]	N=301 Nullipara Included at 20 wk' of pregnancy	2 arm RCT single blind 1. Control: customary information given by their midwife or general practitioner. 2. Intervention: Weekly group training (aerobic training and strength training) in 60 min and daily PFMT (two sets of 8-12 repetitions) as home exercise. General advice related to ergonomics and daily life activities in	Self-reported LPP (once per week or more) Self-reported sick leave Functional ability (DRI)	At 36 wk' of pregnancy LPP: 44 % vs. 56 % (p=0.03) Sick leave: 21 % vs. 25 % (p=0.42) DRI (median): 14 vs. 19 (p=0.01)	12 lost to follow-up Adherence to the exercise protocol was 81 %

				At 3 months postpartum	
		pregnancy. 12 wk' intervention period between 20-36 wk' of pregnancy. Adherence was registered in the personal training diary.		LPP: 26 % vs. 37 % (p=0.06)	
Haugland et al. (2006)[138]	N=560 PGP (verified with clinical tests) Nulli-/multipara Included between 18-32 wk' of pregnancy	2 arm RCT 1. Control: received no intervention but were free to seek advice for their pelvic problem or receive other treatment. 2. Intervention: Educational program in small groups. The groups had one session for 2 h once a week in 4 consecutive wk'. The educational program included general information on PGP, ergonomics, exercises, pain management, advice for daily life movement, demonstration of pelvic belt/crutches/easyslide and information about delivery and the puerperal period.	Pain (VAS) for intensity of pain caused by four daily activities (walking 10 min, standing 10 min, climbing stairs 2 floors, and turning in bed) P4 and symphysis pressure test	6 and 12 months PP: no difference between groups in pain intensity P4 at 6 months PP: 55 % vs. 55 % (p=0.29) P4 at 12 months PP: 80 % vs. 72 % (p=0.92)	60 % of CG received treatment
Granath et al. (2006)[120]	N=390 LPP Nulli-/multipara Included at 11-12 wk' of pregnancy	2 arm RCT 1. Land-based physical exercise (LBPE) 2. Water aerobics (WA) Both interventions focused on strength, flexibility and fitness and consisted of 45 minutes activity followed by 15 minutes of relaxation. The intervention started at 11-12 wk' of pregnancy and continued throughout pregnancy.	Sick leave LPP	LPP: 34/134 in LBPE vs. 19/132 in WA (p=0.04) Sick leave due to LPP: 6/134 in LBPE vs. 0/132 in WA (p=0.03) Sick leave due to any cause, number of days: 9.8 ± 27.6 vs. 6.1 ± 22.4 (p<0.001)	Non-blinded randomization, randomization by date of birth Analysis were done per protocol, 1/3 in each group were excluded from analysis because they did not follow the exercise protocol (266 subjects were analyzed) Average wk' of pregnancy at inclusion was 19 (range 16-29)
Shim et al.	N=62	2 arm cluster-RCT	Pain intensity (VAS)	After 12 wk' intervention	6 lost to follow-up

Study	Population	Design / Intervention	Outcome measures	Results	Comments
(2005)[287]	LPP Included between 17-22 wk' of pregnancy	1. Control 2. Intervention: Back-pain-reducing-program including a standardized education protocol (pamphlet, lecture, audiovisual tape to demonstrate the exercise record, and telephone calls). A 45-minutes educational lecture were held initially and back-pain-reducing-exercises were instructed. Women were encouraged to perform these exercises (following an audiovisual tape, 12 minutes) 5-7x/week for 12 wk'.	Functional limitation (Oswestry Disability Questionnaire) Anxiety (State Anxiety Scale)	Pain intensity: 4 ± 3 vs. 6 ± 2 (p=0.006) Functional limitation: 42 ± 17 vs. 43 ± 15 (p=0.68) Anxiety: 47 ± 5 vs. 48 ± 5 (p=0.19)	No data on adherence Women were not randomized individually
Nilsson-Wikmar et al. (2005)[233]	N=118 PGP (verified with clinical tests) Nulli-/multipara Included until 35 wk' of pregnancy	3 arm RCT 1. Group 1 (G1): information and non-elastic sacroiliac belt. 2. Group 2 (G2): information, non-elastic sacroiliac belt and home exercise program (three stabilizing exercises). 3. Group 3 (G3): information, non-elastic sacroiliac belt and an in clinic exercise program (four strengthening and stabilization exercises, 3 series of 15 repetitions). Performed 2x/week until 39 wk' of pregnancy.	Pain intensity (VAS) Functional ability (DRI)	At 38 wk' of pregnancy VAS: 49 (0-98) in G1 vs. 50 (18-99) in G2 vs. 62 (0-100) in G3 (p=0.82) DRI: 65 (13-92) in G1 vs. 66 (21-91) in G2 vs. 59 (14-91) in G3 (p=0.58) 12 months PP: no significant differences	Randomization stratified according to parity Large differences in the intervention period (ranges from 2-30 weeks). Median wk' from inclusion to gestational week 38 was 10 for G1, 14 for G2 and 16 for G3 <10 % lost to follow-up
Garshasbi and Zadeh (2005)[14]	N=212 Nullipara Included between 17-22 wk' of pregnancy	2 arm RCT 1. Control 2. Intervention: strengthening exercises in groups, 60 minutes, performed 3x/week for 12 wk'.	Pain intensity (KEBEK questionnaire)	After 12 wk' intervention Pain intensity: 31 ± 16 vs. 33 ± 20 (p=0.006)	Women missing ≥3 exercise sessions were excluded from the analysis
Suputtitada et al.	N=67	2 arm RCT 1. Control	Pain intensity (VAS)	After 8 wk' intervention	Only abstract available

Study	Population	Design / Intervention	Outcome measures	Results	Comments
(2002)[302]	Nullipara Included in third trimester	2. Intervention: Sitting pelvic tilt exercises for 8 wk' in the third trimester.		Pain intensity: Lower in IG (p<0.05)	14 lost to follow-up
Kihlstrand et al. (1999)[164]	N=258 Included before 19 wk' of pregnancy	2 arm RCT 1. Control 2. Intervention: Weekly water gymnastics, 60 minutes (30 minutes exercises and 30 minutes relaxation). Women were offered water gymnastics 17-20 times during their pregnancy.	Self-reported LPP Everyday classification of LPP and pain intensity (VAS) Self-reported sick leave	At 34 wk' of pregnancy and within one week of delivery LPP: 71 % vs. 74 % (p=0.57) Significantly lower pain intensity in IG during the 31st and between the 33rd and 38th weeks of pregnancy Sick leave due to LPP during pregnancy: 13 % vs. 22 % (p=0.09) Sick leave 32-33 wk' of pregnancy (n): 7 vs. 17 (p=0.03)	88 % in IG exercised 10-20 times during pregnancy
Norén et at. (1997)[234]	N=135 LBP/PGP Included before 36 wk' of pregnancy	2 arm cluster-RCT 1. Control 2. Five visits with a physiotherapist. Information about anatomy, body posture, ergonomics, gymnastics, PFMT and relaxation. Individual exercise program was designed. Non-elastic pelvic support belt.	Sick leave	During pregnancy Sick leave: 33/54 vs. 45/81 Average days on sick leave: 30.4 vs. 53.6 (p<0.001)	Women were not randomized individually No lost to follow-up
Östgaard et al. (1994)[350]	N=407 PGP/LBP Included before	3 arm RCT 1. Group 1 (G1): standard antenatal care. 2. Group 2 (G2): back school education and a training program (two 45-	Pain intensity (VAS) Sick leave	At 36 wk' of pregnancy Pain intensity: no difference between groups	Randomization according to date of birth 17 % dropout

18 wk' of pregnancy	minutes classes in groups) before 20 wk' of pregnancy. The program included information on anatomy, posture, ergonomics, muscle training and relaxation. 3. Group (G3): back school education, an individualized exercise program (five 30-minutes lessons between 18-32 wk' of pregnancy) and a written home exercises program to be performed 3x/week. The program included information on anatomy, posture, ergonomics, muscle training and relaxation.	Sick leave: 50 % in G1 vs. 52 % in G2 vs. 37 % in G3 (p<0.05)	Per protocol analysis

PubMed search term: ("Pelvic Pain"[Mesh] OR "Back Pain"[Mesh] OR "Pelvic Pain"[tiab] OR "Back Pain"[tiab] OR "Pelvic Girdle Pain"[tiab]) **AND** ("Pregnancy"[Mesh] OR "Pregnancy Complications"[Mesh:NoExp] OR pregnan*[tiab]) **AND** ("Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Physical Fitness"[Mesh] OR "Physical Exertion"[Mesh] OR "Motor Activity"[Mesh] OR "Sports"[Mesh] OR exercis*[tiab] OR training[tiab] OR ("physical activity"[tiab] NOT medline[sb]) **AND** (clinical trial[pt] OR random*[tiab] OR trial[tiab] OR group[tiab] OR groups[tiab] OR systematic[sb]) NOT ((Animals[mesh] NOT Humans[mesh]) OR Case reports[pt])

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CG denotes control group, DRI Disability Rating Index, IG intervention group, LBP low back pain, LPP lumbopelvic pain, PFMT pelvic floor muscle training, P4 Posterior Pelvic Pain Provocation test, PGP pelvic girdle pain, PP postpartum, VAS visual analogue scale.

Incontinence

Definition

Urinary incontinence (UI) is defined as "complaint of involuntary loss of urine", while the term anal incontinence (AI) is defined as "complaint of involuntary loss of feces or flatus".[144] AI can further be divided into fecal incontinence (FI; "complaint of involuntary loss of feces") and flatal incontinence ("complaint of involuntary loss of flatus").[144]

Prevalence of UI

UI is a common condition among women.[213] In a Norwegian cohort study, EPINCONT (N=15,307), the overall prevalence of UI in nulliparous women were 10 %, and the prevalence increases with age.[272] The prevalence of urinary leakage in pregnancy has been reported to vary between 9 % and 74 %.[64,261] This variation is probably due to different study populations (various proportions of nulliparous/parous women), different definitions of incontinence (self-reports or standardized pad tests), different pregnancy lengths, and different definitions. The International Continence Society has changed the definition several times.[3,4,144] In the first standardization of terminology of lower urinary tract function, UI was defined as "involuntary loss of urine which is objectively demonstrable and a social or hygienic problem".[3] As the definition changes, so will the prevalence estimate. Chaliha et al.[64] (N=286) reported a prevalence of 9 % with genuine stress urinary incontinence (SUI) in gestational week 34 measured with urodynamics. Raza-Khan et al.[261] (N=113) included women in the third trimester and registered any type of UI in a questionnaire and reported a prevalence of 74 %.

In the MoBa study including 43,279 women from 1999-2006, 58 % of the women reported any UI and 35 % reported UI weekly or more in pregnancy week 30.[334] The prevalence of UI increased from 26 % before pregnancy to 58 % in pregnancy week 30. The prevalence among nulliparous and parous women was 15 % and 35 % before pregnancy and 48 % and 67 % at 30 weeks.[334] A cohort of nulliparous women (N=1,128), who were continent before pregnancy, reported an UI incidence of 39 % at some point during pregnancy.[292] Another observational study of primiparous women (N=1,501) found that 4 % reported UI before

pregnancy and 38 % during pregnancy.[187] In both studies the incidence of UI was low in the first trimester, rising rapidly in the second trimester and continued to rise more slowly in the third trimester.[187,292] In a third cohort of nulliparous women (N=1,507), 11 % reported UI at least once per month before pregnancy, and the prevalence increased to 17 % in early gestation and 56 % in the third trimester of pregnancy.[44] In all three studies the severity increased slightly with increasing gestation.[44,187,292] A correlation between severity of UI and level of interference in daily living was found.[292]

The increase in UI during pregnancy is mainly due to incidence of SUI.[187,292] The prevalence of pure SUI is reported to be 1.7-8 times higher than the prevalence of pure urgency urinary incontinence (UUI) in pregnancy. Prevalence of mixed UI is reported to be 0.2-2.2 times of the prevalence of pure SUI in pregnancy.[44,118,187,261]

In a systematic review including 33 studies on UI postpartum, a pooled prevalence of any UI postpartum was found to be 33 %, with weekly UI to be 12 % and daily UI 3 %.[310] There were only small changes in the prevalence of UI over the first year postpartum.[310]

Risk factors for UI
Data suggest that pregnancy contributes to pelvic floor dysfunction later in life.[194] The precise etiology of UI in pregnancy is unknown, but there is a variety of changes associated with pregnancy, e.g. hormonal and mechanical changes that could contribute.[154] Prenatal physiological changes such as increases in intra-abdominal pressure of the growing uterus and fetal weight on the PFM throughout pregnancy together with pregnancy-related hormonal changes may lead to reduced strength and reduced supportive and sphincter functions of the PFM.[148]

Incontinence during pregnancy has been linked to age,[274] BMI,[131] strenuous physical exercise,[102] smoking history,[131] and a family history of UI.[292] In the EPINCONT study Rørtveit et al.[274] found that women having their first baby after the age of 25 had higher prevalence of UI than women having their first baby before the age of 25 (28 % versus 23 %, p<0.01). However, the effect attenuated with increasing actual age, and it disappeared in the age group 50 to 64 years.[274]

Developing de novo SUI during pregnancy was associated with BMI >30.[187] In the MoBa study weight gain in pregnancy does not seem to be a clinically important risk factor for UI. However, weight loss postpartum may be important for regaining continence 6 months postpartum.[333] Brown et al.[44] found that women with subclinical urinary symptoms before pregnancy, younger women (18-24 years), older women (≥40 years), and those with a BMI ≥30 were at an increased risk of developing de novo UI in pregnancy. The factor most strongly associated with the onset of UI during pregnancy was the presence of occasional leakage of urine before pregnancy.[44] Solans-Domenech et al.[292] found that the risk of UI increased in pregnant women >35 years, with overweight or obesity at baseline and a family history of UI. Hannestad et al.[130] found that women were more likely to develop UI if their mother or older sisters were incontinent, suggesting that a genetic predisposition plays a role in the development of UI.

Antenatal UI is found to be a risk factor for UI postpartum, and many authors have found that UI in pregnancy is an important predictor for UI later in life.[48,91,110,155,286,319,324,332] A history of UI prior to pregnancy significantly increases the chance that postpartum UI will persist.[104,294] In a cohort study it was found that most women experiencing postpartum UI had symptoms of UI during the third trimester.[261] Another study found that five years after the first delivery, 33 % of women reported UI.[323] In a twelve year prospective study, Viktrup et al.[324] found that in women with onset of UI in pregnancy or shortly after their first delivery had increased risk of long-lasting symptoms. Among women who were continent during their first pregnancy and the postpartum period, the prevalence of UI 12 years after the first delivery was 33 % compared to 66 % in women who became incontinent during their first pregnancy and the postpartum period.[325]

In the EPINCONT study including 27,936 women, the reported prevalence of any UI was 25 % in the adult population, with the prevalence of incontinence increasing with age.[132] In the Women's Health Australia Project, including three age cohorts of women completed in 1996, women were asked if they had experienced leaking urine last year. The estimated prevalence of UI in young women (18-23 years, N=14,000) was 13 %, middle-aged women (45-50 years, N=13,738) 37 % and old women (70-75 years, N=12,417) 35 %.[71] Middle-aged and older nulliparous women were almost three times more likely to report UI than nulliparous young women. UI was significantly associated with parity, constipation, obesity, past gynecological

surgery and conditions which can impact on bladder control, such as coughing and sneezing on a regular basis.[71] In twin studies it has been found that women (mean age 47 years) with at least two births are four times more likely to report UI than their nulliparous twin sisters.[117] Among premenopausal women, parous women have higher prevalence of UI than nulliparous women.[273] Among postmenopausal women, a history of pregnancy and childbirth has little impact on the prevalence of UI. Old nulliparous women are as likely to have UI as parous women.[43,273] It is assumed that other factors, such a comorbid medical conditions and age-related changes, outweigh the effect of previous pregnancies.[235] The numbers of striated muscle fibers of the urethral sphincter decrease with age and parity, with an average loss of 2 % per year from 15 to 80 years of age.[19] In an epidemiological study it was found that 50 % of incontinence can be attributed to pregnancy and childbirth among parous women.[248] However, there are many unanswered questions, and the available literature cannot distinguish the effects of pregnancy from the effects of childbirth.

High BMI and the presence of antenatal UI are modifiable risk factors. The presence of these risk factors may help clinicians target at-risk women for early intervention.

Prevalence of AI

In a review of 16 studies, the estimated prevalence of AI varied from 2-24 %, and the estimated prevalence of FI varied from 0.4-18 % in community-dwelling adults.[195] AI is less studied in pregnancy, but the prevalence of AI has been found to increase from pre-pregnancy to late pregnancy.[65,66,292] Prevalence rates for AI before, during, and after the first pregnancy of 0-1 %, 0-8 %, and 2-26 % have been reported.[65,126,191,192,284,301,306,318,346] The presence of AI is mainly characterized by loss of flatus in more than 90 % of cases.[292]

The prevalence of AI postpartum has been reported to be 9 % - 27 %.[66,101,113,288,301]

Risk factors of AI

Pregnancy and delivery are risk factors for AI in later life,[47] and the first pregnancy and delivery is associated with a high prevalence of objective and subjective bowel dysfunction.[66] Age and excess weight gain during pregnancy are associated with the occurrence of AI during

pregnancy,[292] however, risk factors for development of AI during pregnancy have been sparsely studied.

In twin studies, it has been found that women (mean age 47 years) with at least two births are three times more likely to report AI than their nulliparous twin sisters.[2] Obstetric trauma is one of the major causes of AI in women. During delivery a sphincter trauma and/or pudendal neuropathy can occur. Risk factors for sphincter injury are vaginal birth, midline episiotomy, forceps delivery and vacuum-assisted delivery.[101] A review including 18 studies found that symptoms of AI in the first year postpartum were associated with the mode of delivery.[258] Women with spontaneous delivery had increased risk of AI postpartum compared to cesarean delivery (OR 1.32, 95 % CI 1.04-1.68). In forceps deliveries, women had doubled risk of AI compared to cesarean delivery (OR 2.01, 95 % CI 1.47-2.74).[258] Solans-Domenech et al.[292] identified AI during pregnancy and vaginal delivery as risk factors for AI postpartum. Women with FI de novo postpartum are more likely to have had a third or fourth degree anal sphincter rupture (OR 8.0, 95 % CI 4.6-13.8).[318] A systematic review including 31 longitudinal studies found that third- or fourth-degree sphincter rupture was the only etiological factor strongly associated with postpartum AI.[38] A meta-analysis included five studies with a total of 717 women who underwent an endoanal ultrasonography to diagnose anal sphincter defects following a vaginal delivery.[237] The study reports an incidence of 27 % anal sphincter defects in primiparous women and an incidence of 9 % new sphincter defects in multiparous women. Overall, 30 % of anal sphincter tears had symptoms, and 3 % of women experienced postpartum FI without anal sphincter defect.[237]

Incontinence and quality of life
In one prospective study (N=597), 42 % and 19 % reported SUI and UUI in gestational week 36, of those only 6 % and 3 % reported it to be causing bother.[320] Although UI is common, it reduces quality of life and affects social, physical, occupational and leisure activities.[156]

AI is less prevalent than UI, but this condition is clearly a social and psychological burden with a significant impact on quality of life.[108,129,150,189] FI further reduces quality of life in women with UI,[108] and FI and UI together have a greater impact on quality of life than either condition alone.[129] Women affected by moderate or severe FI may suffer embarrassment,

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social isolation, curtailed activities, and severely impaired quality of life.[31] Despite the negative effect on quality of life, few women discuss AI with their medical providers.[189] In a cohort study (N=906) women were asked about FI symptoms 10 months after birth, and 36 (4 %) reported new FI after birth. In all, 27 (75 %) of 36 women had symptoms several times a week, however only five consulted a doctor.[191] FI symptoms are known to be underreported.[186,191] The reason may be embarrassment, but could also be little knowledge about treatment.

Anatomy of the pelvic floor

The pelvic floor (PF) is an important part of the continence mechanisms.[19] The PF consists of several components between the pelvic peritoneum and the vulvar skin. These are (from above downwards) the peritoneum, viscera and endopelvic fascia, levator ani muscles, perineal membrane, and external genital muscles.[86] The pelvic organs (vagina, bladder and rectum) are ensured by fascias and ligaments.

The levator ani group of muscles (Figure 3A and 3B) keeps the urogenital hiatus closed.[86] The different muscles have different fiber directions, and if each muscle could contract in isolation, they would all have different functions. However, the only known voluntary function of the PFM is a mass contraction best described as an inward lift and squeeze around the urethra, vagina and rectum.[57] The levator ani muscles have constant activity, like that of other postural muscles.[86] In addition, the PFM close the PF and carry the weight of the abdominal and pelvic organs, preventing constant strain on the ligaments.[86] As long as the levator ani muscles function properly, the PF is closed and the ligaments and fascia are under no tension; the fasciae simply act to stabilize the organs in their position above the levator ani muscles. In continent women an automatic (unconscious) co-contraction occurs when abdominal pressure increases.[50] The amount of striated muscle declines considerable with age[251] and is associated with a decline in innervating nerves.[245]
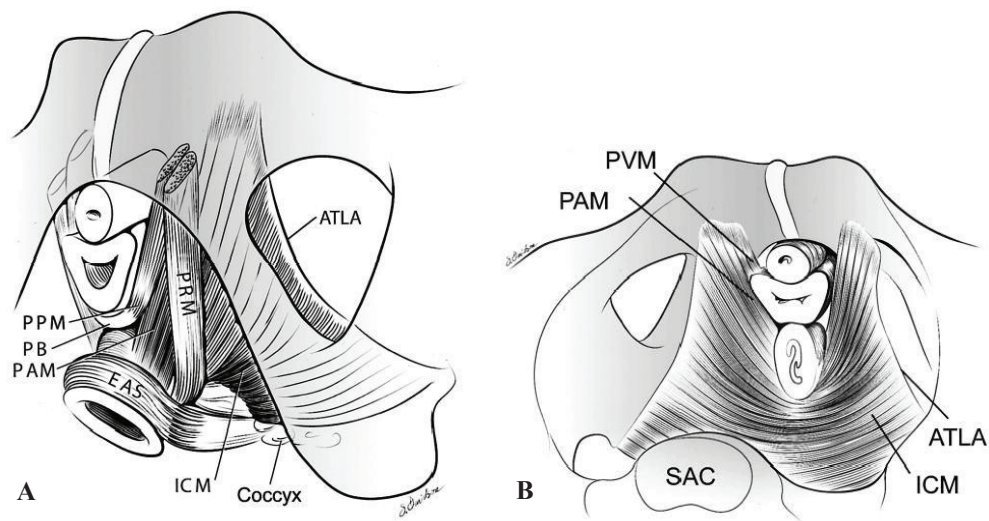
Figure 3A. Schematic view of the levator ani muscles from below after the vulvar structures and perineal membrane have been removed showing the arcus tendineus levator ani *(ATLA)*; external anal sphincter *(EAS)*; puboanal muscle *(PAM)*; perineal body *(PB)* uniting the 2 ends of the puboperineal muscle *(PPM)*; iliococcygeal muscle *(ICM)*; puborectal muscle *(PRM)*. Figure 3B. The levator ani muscle seen from above looking over the sacral promontory *(SAC)* showing the pubovaginal muscle *(PVM)*. The urethra, vagina, and rectum have been transected just above the pelvic floor. *PAM* = puboanal muscle; *ATLA* = arcus tendineus levator ani; and *ICM* = iliococcygeal muscle. Printed with permission from John O.L. DeLancey©.

The lower urinary tract is composed of the bladder and urethra. They form a functional unit and their interaction cannot be ignored. Each has two functions, the bladder to store urine and void, the urethra to control and convey.[3] Urethral closure pressure must be greater than bladder pressure, both at rest and during increases in abdominal pressure to retain urine in the bladder.[19] During activities, such as coughing, when bladder pressure increases several times higher than urethral pressure, a dynamic process increases urethral closure pressure to enhance urethral closure and maintain continence. This is referred to as "pressure transmission". Both the magnitude of the resting pressure in the urethra and the increase in pressure generated during a cough determine the pressure at which a leakage of urine occurs.[19]

Anal continence depends on several anatomic and physiologic entities such as the anal sphincter function, PF function, rectal distensibility, anorectal sensation, anorectal reflexes,

intact nervous system, mental function, stool volume, stool consistency, and colonic transit. Deficiency in one or more of these factors can lead to AI.[196] The anal sphincter muscles are located in the distal part of the anal canal. The anal sphincter involves the internal anal sphincter, external anal sphincter and puborectalis muscle.[196]

In the non-pregnant women, the uterus is an almost solid structure weighing about 70 g and with a cavity of 10 ml or less. During pregnancy, the uterus is transformed to accommodate the fetus, placenta, and amnionic fluid. The total volume of the contents at term averages about 5 l, but may be up to 20 l or more. By the end of pregnancy, the uterus has achieved a capacity that is 500 to 1000 times greater than in the non-pregnant state.[80] In late gestation, the fetal head markedly alters bladder geometry.[90]

Pregnancy and delivery are associated with functional and anatomical changes in the muscles, nerves, and connective tissue of the PFM.[128] In women with de novo SUI after their first birth, injury to the levator ani muscle is found twice as often as in women who are continent after delivery.[87] The first vaginal delivery also results in changes in EMG patterns of striated sphincter musculature that is consistent with impaired muscular function persisting for at least six months beyond delivery.[331] Deindl et al.[85] compared parous women with SUI (n=8) and nulliparous continent women (n=10) with EMG-measures of the PFM. The muscle activation pattern was in principle similar except for lower holding time in a voluntary pelvic floor muscle contraction (VPFMC) and asymmetric and uncoordinated activity pattern in the levator ani muscles among parous incontinent women.[85] Mørkved et al.[227] (N=103) assessed muscle strength and thickness in nulliparous pregnant women at 20 weeks of gestation, and found higher maximal vaginal squeeze pressure and increment in muscle thickness in continent compared to incontinent women.

Pelvic floor muscle training
Pelvic floor muscle training (PFMT) for the treatment of UI was popularized by the American gynecologist Arnold Kegel in 1948.[162] However, PFMT has been a part of exercise programs in Chinese Taoism for over 6000 years.[99] PFMT has been found to have a high cure rate in the adult female population and is recommended as first line treatment for women with SUI, UUI or mixed incontinence.[99] There are two hypothesis explaining the effect of PFMT; behavior

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modification and increased muscular strength. The rationale for teaching women how to perform a conscious contraction of the PFM before and during increases in abdominal pressure,[212] is that the urethra and bladder base is prevented from descending.[50] Miller et al.[212] found that 80 % of women with de novo SUI in pregnancy week 35 were able to reduce leakage during coughing by using the Knack maneuver (i.e. tighten the PFM in preparation for a known leakage-provoking event), with 55 % eliminating leakage completely. Neural adaptations can explain increases in muscle function before hypertrophy occurs. This effect is related to motor learning, since the more motor units that are recruited, the better will be muscle function.[263] Strength training of the PFM builds up muscle volume, elevates the location of the PFM and pelvic organs, and closes the levator hiatus thus providing improved structural support for the PF as well as more optimal automatic function.[51] Morphological changes such as increased muscle thickness (Figure 4), narrowed resting area of the levator hiatus, reduced puboviceral length and elevated resting position of the bladder and the rectal ampulla after PFMT have been documented after an intensive PFMT program.[45] The functional changes (elevated resting position of the bladder and rectum and the reduced pubovisceral length and hiatus size at maximum Valsalva) may be explained by increased "stiffness" in the muscle-connective tissue complex.[45] During pregnancy the growing uterus will compress the bladder. Strengthening the PFM results in better structural support for the bladder neck and a strong contraction of the PFM ensures continence during an abrupt increase in the abdominal pressure.[50]
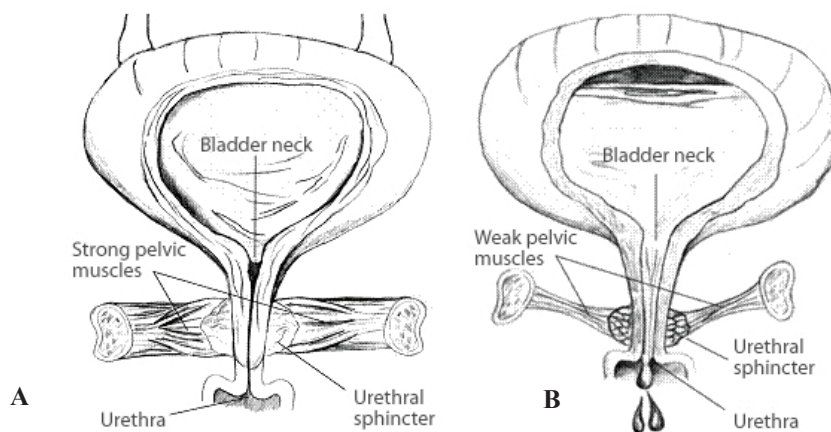

Figure 4. Illustration of an optimal (A) and non-optimal (B) pelvic floor muscle. (http://96.127.164.163/pelvic_muscles.html)

The influence of PFMT on UI and AI

A variety of hypotheses have been suggested about why PFMT might help prevent and treat incontinence in pregnancy and after delivery. A trained muscle might be less prone to injury, and previously trained muscles might be easier to retrain after damage as the appropriate motor patterns are already learned. It may be that previously trained muscle has a greater reserve of strength so that injury to the muscle itself, or its nerve supply, does not cause sufficient loss of muscle function to reach the threshold where reduced urethral pressure results in leakage.[141] During pregnancy, training the PFM might help to counteract the increased intra-abdominal pressure caused by the growing fetus, the hormonally mediated reduction in urethral pressure, and the increased laxity of fascia and ligament in the pelvic area. A similar rationale might be used to support the use of PFMT to improve the function of the external anal sphincter and thus prevent AI.[141]

In a systematic literature search on PubMed (Table 4) three previous trials were found addressing primary prevention of UI during pregnancy.[119,200,262] Four trials included both continent and incontinent women in pregnancy.[54,171,226,279] Three trials have assessed the effect of treatment of UI during pregnancy.[92,282,340] No previously published trial addressing primary prevention of AI was found. One previous trial included PFMT in a general fitness program for pregnant women.[54] This trial demonstrated that there was no difference in UI or AI between intervention and control groups. However, this trial had some limitations such as being underpowered, including no control of the women's ability to perform a correct VPFMC, high dropout rates and low adherence to the exercise training protocol.[54]

Common for all trials with a positive effect of PFMT are that they are based on thorough clinical assessment of the participants' ability to contract the PFM correctly, had close follow-up of the pregnant women either in groups or individually, and had high adherence to the exercise protocol. In contrast, trials with no effect had an inadequate training dosage, left the patients alone to train or had low adherence to the exercise protocol. As for all other strength training regimens, the effects of PFMT are dependent on the training dosage and adherence to training. Type of exercise, frequency, intensity and duration of the training in addition to the adherence to the exercise protocol will decide the effect size.[55,136] The concept of intensive PFMT was introduced by Bø et al.[55] The recommendations for effective strength training to

increase muscle cross-sectional area and strength are 3 sets of 8-12 close to maximum contractions 3-4 times a week.[136]

The success of training depends on the ability to effectively contract the PFM. It is estimated that 30 % of women are unable to contract the PFM on the first attempt.[46,56] Bump et al.[46] found that only 49 % performed an ideal VPFMC after brief standardized verbal instruction, and Dinc et al.[92] found that only 68 % of pregnant women were able to perform a correct VPMFC one week after individual thorough instruction. Vaginal palpation is most commonly used by physiotherapist to evaluate the function and strength of the PFM, however ultrasound is a more objective measure and is becoming an important clinical tool.[58]

RCT's have documented the effects of intensive PFMT and close follow-up of physiotherapists in the prevention and treatment of pregnancy-related UI.[92,119,171,226,262,279,282] A Cochrane review addressing the prevention of urinary- and fecal incontinence included mixed prevention and treatment trials.[141] This review concluded that continent women randomized to intensive PFMT were 56 % less likely to report UI in late pregnancy and about 30 % up to six months postpartum.[141] Nevertheless, the Cochrane review and two other systematic reviews conclude that the effect of PFMT during pregnancy to prevent UI and AI is still open to question.[42,141,225] The Cochrane review strongly recommends that all future trials of PFMT during pregnancy should collect data on AI, and highlights the need for large, pragmatic trials with population-based approaches, using intensive PFMT and recruiting antenatal women regardless of continence status or parity.[141] There is a lack of trials investigating the effect of implementing PFMT in a more general training program for pregnant women. The cost of illness for incontinence is a substantial economic and human burden, highlighting the need for effective forms of management.[213] The importance of effective prevention is obvious.

Table 4. Randomized controlled trials assessing the effect of pelvic floor muscle training during pregnancy to prevent and treat incontinence including both women with and without incontinence at inclusion.

Author	Subjects	Design / Intervention	Outcome	Results (IG vs. CG)	Comments
Sangsawang et al. (2011)[282]	N=70 Nulli-/multipara SUI (≥1 episode of urinary leakage last month) Included between 20-30 wk' of pregnancy	Quasi-experimental study, pre-post test with control group 1. Control: usual nursing care (including written instructions in PFMT). 2. Intervention: written and individual oral instruction in correct VPFMC (no vaginal palpation, but instructions in "stop-test" i.e. trying to stop or slow urinary flow) and PFMT. PFMT (45 minutes) in groups every second week for 6 wk'. Home exercises, with 40 repetitions daily, 5 x/week (slow contractions with 10 second holding time and 10 fast contractions at the end of holding time). Performing PFMT was recorded in a training diary.	SUI severity (frequency and amount) SUI severity (VAS)	After 6 wk' intervention: No leakage: 39 % vs. 0 % (p=0.001) Frequency SUI: 2 ± 4 vs. 15 ± 10 (p<0.001) Severity SUI (VAS): 1.3 ± 1.3 vs. 6.8 ± 2.2 (p<0.001)	Women in the IG were matched to CG women regarding age, parity and severity of SUI Women who failed to perform PFMC were categorized as dropout 4 lost to follow-up in IG No assessment of correct VPFMC 100 % in IG adhered to the exercise protocol (≥28 days of PFMT)
Bø and Haakstad (2011)[54]	N=105 Nullipara Continent/ incontinent Sedentary Included within 24 wk' of pregnancy	2 arm RCT 1. Control 2. Intervention: attending aerobic fitness classes including PFMT, 2-3x/week, and performing 10 daily PFMC at home. The PFMT instructed in classes consisted of three sets of close to maximum contractions of 8-12 repetitions with holding periods of 6-8 seconds performed in different positions. Women were encouraged to be physically active ≥30 minutes daily. Intervention period was 12-16 wk'.	UI and AI reported in a personal interview	At 36-38 wk' of pregnancy UI: 17/42 vs. 16/42 (p=0.82) Flatus: 11/42 vs. 9/16 (p=0.61) AI: 1/42 vs. 1/42 At 6-8 wk' PP UI: 12/43 vs. 13/47 (p=0.99) Flatus: 10/43 vs. 8/47 (p=0.46) AI: 1/43 vs. 3/47 (p=0.62)	No assessment of correct VPFMC Classes led by an aerobic instructor, verbal instructions were given 40 % of IG women attended at least 80 % of the exercise sessions 20 % were lost to follow-up No data on level of exercise and PFMT in the CG
Ko et al.	N=300	2 arm RCT	UI reported in a personal	At 36 wk' of pregnancy:	Adherence (defined as

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Study	Population	Design/Intervention	Outcome measure	Results	Comments
(2011)[171]	Nullipara Continent/incontinent Included between 16-24 wk' of pregnancy Performing PFMT was an exclusion criteria	1. Control: received regular prenatal care. 2. Intervention: weekly PFMT in group led by a physiotherapist (45 min). And daily home exercises (three repetitions of 8 contractions each held for 6 seconds) performed twice daily. Women were individually instructed in anatomy and correct VPFMC (by observation of inward movement of perineum during contraction).	interview Incontinence Impact Questionnaire (IIQ-7) Urogenital Distress Inventory (UDI-6)	34 % vs. 51 % (p<0.01) At 3 days PP: 30 % vs. 41 % (p=0.07) At 6 wk' PP: 25 % vs. 35 % (p=0.06) At 6 months PP: 16 % vs. 27 % (p=0.04) The IG had lower scores in total UDI-6 and IIQ-7 than CG in late pregnancy and PP No differences in pregnancy outcome	performing ≥75 % of PFMT) was 87 % No lost to follow-up
Mason et al. (2010)[200]	N=311 Nullipara No previous SUI Included between 11-14 wk' of pregnancy	2 arm RCT single blind 1. Control: usual care and instructions in PFMT. 2. Intervention: attending a physiotherapy class (45 minutes) with PFMT 1x/month for four months and to perform daily PFMT at home (8-12 close to maximum PFMC each held 6-8 seconds twice daily). Individual assessment of correct VPFMC was performed in most women.	Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS) Leicester Impact Scale (LIS) Self-reported number of leakage episodes last three days	UI at 36 wk' of pregnancy: 24/60 (40 %) vs. 51/96 (53 %) (p=0.14) UI at three months PP: 23/68 (33.8 %) vs. 33/80 (41.3 %) (p=0.40) No sig difference in symptoms and episodes of UI between groups in late pregnancy and PP	8 % were lost to follow-up. 23 % failed to return any of the questionnaires, and only 31 % completed all three sets of questionnaires Only 65 % of IG women attended ≥1 exercise class The trial was underpowered
Dinc et al. (2009)[92]	N=92 Nulli-/multipara Incontinent (having	2 arm RCT 1. Control 2. Intervention: Thorough instructions in correct PFMC and a home exercise program with gradually increasing repetitions and holding time until	Self-reported UI	UI at 36-38 wk' of pregnancy: 43.2 % vs. 71.4 % UI at 6-8 wk' PP: 17.1 % vs. 38.4 %	12 lost to follow-up Correct VPFMC checked at enrolment in both groups

	complaints of stress/mixed UI in their history) Included between 20-34 wk' of pregnancy	three sets of 15 repetitions with 10 seconds holding time and fast contractions added, repeated 3x/day.		Significant difference in episodes of UI, urgency, number of voids and amount of urine in pad test in favor of the IG both at 36–38 wk' pregnancy and at 6-8 wk' PP	
Woldringh et al. (2006)[340]	N=264 Incontinent (≥2 episodes of loss of urine last month) Nulli-/multipara Included between 17-20 wk' of pregnancy	2 arm RCT 1. Control: routine care. 2. Intervention: Four sessions of individual PFMT; three sessions (with 2 week interval) between 23-30 wk' of pregnancy and a fourth session 6 wk' PP. Written information including a detailed PFMT program.	Self-reported severity of UI Incontinence Impact Questionnaire (IIQ)	No difference between IG and CG with respect to the severity of UI and impact of UI on daily life	No vaginal palpation of VPFMC, but observation and palpation of the perineal body 50 % lost to follow-up Low adherence, only 37 % reported to exercise almost every day
Gorbea Chavez et al. (2004)[119]	N=72 Nullipara Continent	2 arm RCT 1. Control: no PFMT. 2. Intervention: individual PFMT with physiotherapist. 10 PFMC each held for 8 seconds and followed by 3 fast contractions weekly for 8 wk', then weekly phone calls up to 20 wk'. Biofeedback and training diary. Individual assessment of correct VPFMC was performed.	Self-reported UI	UI at 28 wk' of pregnancy: 0 % vs. 17.2 % (p<0.05) UI at 35 wk' of pregnancy: 0 % vs. 47 % (p<0.05) UI at 6 wk' PP: 15 % vs. 47 % (p<0.05)	Only abstract available
Morkved et al. (2003)[226]	N=301 Nullipara	2 arm RCT single blind 1. Control: customary information given by their midwife or general practitioner. Correct VPFMC	Self-reported UI (women reporting UI ≥1/week were categorized as incontinent)	UI at 36 wk' of pregnancy: 32 % vs. 48 % (p=0.07)	Low dropout rate, 4 % Adherence 81 %

Study	Design/Intervention	Outcome	Results	Comments
Continent/ incontinent Included at 20 wk' of pregnancy	checked at inclusion. 2. Intervention: 12 wk' weekly PFMT in groups led by physiotherapist, with additional home exercises (10 close to maximum PFMC each held for 6 seconds, 3–4 fast contractions added on the last 4 exercises. Repeated 2x/day). Intervention period between 20-36 wk' of pregnancy. Correct VPFMC checked at inclusion.		UI at 3 months PP: 20 % vs. 32 % (p=0.02)	
Reilly et al. (2002)[262] N=268 Nullipara Continent with increased bladder neck mobility Included at 20 wk' of pregnancy	2 arm RCT 1. Control: routine antenatal care likely to include verbal instructions in PFMT. 2. Intervention: Individual PFMT with physiotherapist at monthly intervals from 20 wk' of pregnancy until delivery, with additional home exercises. 3 sets of 8 contractions (each held for 6 seconds), repeated twice daily. At 34 wk' of pregnancy the number of contractions per set was increased from 8 to 12. Women were instructed to contract the PFM when coughing or sneezing. Performing PFMT was recorded in a personal training diary.	Self-reported UI	UI at 3 months PP: 19 % vs. 33 % (p=0.02)	14 % lost to follow-up 46 % IG women performed PFMT ≥28 days
Sampselle et al. (1998)[279] N=72 Nullipara Continent/ incontinent Included at 20 wk' of pregnancy	2 arm RCT single blind 1. Control: routine care. 2. Intervention: PFMT tailored to the woman's individual ability, with muscle identification exercises preceding strength-building efforts. 30 PFMC daily at maximum or near-maximum intensity was recommended for strength building. Correct VPFMC were checked.	Self-reported UI (results reported as change in mean UI symptom score)	At 35 wk' of pregnancy: Less UI symptoms were seen in the IG vs. CG (p=0.04) At 6 wk' PP: Less UI symptoms were seen in the IG vs. CG	Adherence 85 % Study participants were financially compensated, $150

59

	(p=0.03)
	At 6 months PP:
	Less UI symptoms were seen in the IG vs. CG (p=0.04)

PubMed search term: (exp Pregnancy OR Puerperal Disorders[mesh:noexp] OR Pregnan*[tiab] OR maternal[tiab] OR gravidity[tiab] OR gestation[tiab] OR "after delivery"[tiab] OR "post delivery"[tiab] OR post-partus[tiab] OR post-partum[tiab] OR postpartus[tiab] OR postpartum[tiab] OR "post labor"[tiab] OR postnatal*[tiab] OR prenatal*[tiab] OR antenatal*[tiab] OR childbirth[tiab] OR childbearing[tiab] OR "child bearing"[tiab]) AND (Pelvis[mesh] OR pelvis[tiab] OR pelvic[tiab]) AND (Exercise therapy[mesh] OR Exercise[mesh] OR Exercise Movement Techniques[mesh] OR exercis*[tiab] OR strengthen*[tiab] OR training[tiab]) AND (Urinary Incontinence[mesh] OR Enuresis[mesh] OR ((urine[tiab] OR urinary[tiab]) AND (continen*[tiab] OR incontinen*[tiab] OR leak*[tiab] OR wetting[tiab])) OR Fecal Incontinence[mesh] OR Flatulence[mesh] OR flatulence[tiab] OR ((fecal[tiab] OR feces[tiab] OR flatal[tiab] OR anus[tiab] OR anal[tiab]) AND (continen*[tiab] OR incontinen*[tiab] OR leak*[tiab])) AND (Clinical trial[pt] OR random*[tiab] OR trial[tiab] OR group[tiab] OR groups[tiab])

AI denotes anal incontinence, CG control group, IG intervention group, PFMC pelvic floor muscle contraction, PFMT pelvic floor muscle training, PP postpartum, RCT randomized controlled trial, SUI stress urinary incontinence, UI urinary incontinence, VAS visual analogue scale, VPFMC voluntary pelvic floor muscle contraction.

AIMS OF THE THESIS

A general aim of this thesis was to evaluate the efficacy of regular exercise during pregnancy in the prevention of pregnancy-related diseases and complications during labor.
More specifically, the aims of the separate papers were:

Study I

To assess the efficacy of offering pregnant women a regular exercise program to prevent GDM and improve insulin resistance.

Study II

To assess if women randomized to a regular exercise program were more likely to report LPP than women receiving standard antenatal care.

Study III

To assess if pregnant women following a general exercise course including PFMT, were less likely to report UI and AI in late pregnancy than a group of women receiving standard antenatal care.

Study IV

To assess whether the energy expenditure recorded with the physical activity monitor SenseWear[TM] Pro$_2$ Armband differs from that recorded with indirect calorimetry in pregnant women.

MATERIAL AND METHODS

Study design

A two-armed, two-center RCT (Training in Pregnancy (TRIP) trial) of a 12-week regular exercise program was conducted and compared with standard antenatal care. Pre-tests were done at 18-22 weeks and post-tests at 32-36 weeks of pregnancy.

Concealed randomization in blocks of 30 was performed at the Unit for Applied Clinical Research, Norwegian University of Science and Technology, by a web-based computerized procedure. The randomization was undertaken separately for each hospital to ensure that both sites would have approximately 50 % of their participants in each group. The staff involved with training or outcome assessments had no influence on the randomization procedure. Because of the nature of the study it was not blinded.

Study population

Studies I-III

Pregnant women booking for routine ultrasound scan at St. Olavs Hospital, Trondheim University Hospital and Stavanger University Hospital were invited to participate in the trial. Women in Trondheim were recruited from April 2007 to June 2009, and women in Stavanger were recruited from October 2007 to January 2009. During the study period approximately 12,000 women had a routine scan at the two hospitals. All women were invited with written information about the study attached to the invitation letter for the routine ultrasound scan.

Women willing to participate were asked to contact the project coordinator. Inclusion criteria were Caucasian women aged ≥18 years with a singleton live fetus. Exclusion criteria were high-risk pregnancies and/or diseases that could interfere with participation (Appendix 1). For

practical reasons we also excluded women who lived too far from the hospitals to attend weekly training groups (more than a 30 minute drive). Fewer than 10 % (N=875) of the approximately 12,000 women attending routine ultrasound scans at the two hospitals during the study period, were recruited into this trial. The two hospitals are serving large geographical catchment areas, and the numbers of women from eligible geographical areas were obviously lower than 12,000. The exact number of women who met all the inclusion criteria and were eligible for this study, is not known.

Table 5. Comparison of women included in the TRIP trial with a sample of general pregnant population.

	TRIP (N = 855)	Sample of the general pregnant population (N = 177)	P-value*
Parity			0.69
0	57 %	59 %	
1	30 %	27 %	
2+	14 %	14 %	
Pre-pregnancy weight – kg	65.8 ± 9.9	67.5 ± 14.1	0.14
Pre-pregnancy BMI – kg/m^2	23.1 ± 3.2	23.9 ± 4.8	0.04
Booking weight – kg	70.6 ± 10.1	72.3 ± 13.9	0.14
Booking BMI – kg/m^2	24.8 ± 3.2	25.7 ± 4.9	0.03
Exercised regularly pre-pregnancy	71 %	62 %	0.02
Exercised regularly ≥3x/week at moderate to high intensity pre-pregnancy	32 %	32 %	0.85
Exercise regularly at 18 weeks	52 %	49 %	0.50
Exercise regularly ≥3x/week at moderate to high intensity at 18 weeks	13 %	20 %	0.01

*Equal variances were not assumed in order to obtain a more conservative estimate between groups.
Data are mean ± standard deviation or %.
BMI denotes Body Mass Index.

To assess whether the population in the TRIP trial was representative of the general population of pregnant women, all women attending a routine ultrasound scan at St. Olavs Hospital during a two month period in spring 2009, were asked to anonymously fill in a questionnaire covering baseline characteristics and levels of exercise (pre-pregnancy and at the time of the scan). Women were asked about the type, frequency and intensity of exercise. The questions were similar to those included in the main questionnaire of the trial. A total of

177 women filled in the questionnaire and they were compared with women included in the TRIP trial (Table 5).

Women included in the TRIP trial were also compared with women enrolled in the MoBa study[232,244] and all births registered in the Medical Birth Registry in 2009[229] (Table 6).

Table 6. Comparison of women included in the TRIP trial with women included in the MoBa study and all births registered in the Medical Birth Registry in 2009.

	TRIP (N = 855)	MoBa (N = 73,579)	Medical birth registry (N = 62,991)
Age – years	30.4 ± 4.4	30.0 ± 4.6	29.7 ± 5.3
Parity			
0	57 %	43 %	43 %
1	30 %	36 %	35 %
2+	14 %	21 %	22 %
Marital status			
Single	2 %	4 %	10 %
Married/cohabitant	98 %	96 %	90 %
Booking BMI* – kg/m^2	24.8 ± 3.2	25.2 ± 4.2	-
Birth weight – g	3579 ± 540	3570 ± 611	3478 ±627
Gestational age at birth – weeks	40.0 ± 1.8	39.3 ± 2.2	39.3 ± 2.3
Exercised regularly ≥3x/week at moderate to high intensity pre-pregnancy†	32 %	46 %	-
Exercise regularly ≥3x/week at moderate to high intensity at inclusion*†	13 %	28 %	-

*Women in the MoBa study filled in the questionnaire in gestational week 17 and women in the TRIP trial in gestational week 18-22.
†Data from the MoBa study was based on 34,508 women enrolled in 2001-2005.
Data are mean ± standard deviation or %.
BMI denotes Body Mass Index.

The MoBa study included 43.5 % of all eligible women.[232] Since our results are comparable with the MoBa Study and the Medical Birth Registry, we find the external validity of the trial to be acceptable for Norway. However, the generalizability of the results should be interpreted with caution in other pregnant populations with higher BMI, less physically active women and in ethnically diverse populations.

Study IV

During a period of two months, women included in the RCT were also asked to participate in a study aiming to validate a physical activity monitor (SenseWear[TM] Pro$_2$ Armband). Twenty-nine pregnant women (24–43 years old) in the second (*n*=13) and third trimester (*n*=16) were recruited. None of the participating women used medications or smoked, which could have influenced the energy expenditure.

Intervention

Studies I-III

Women in the intervention group were encouraged to exercise three days per week during the 12-week intervention period. They received a standardized exercise program including aerobic activity, strength training and balance exercises. The training protocol followed recommendations from the ACOG and the Norwegian National Report on Physical Activity and Health.[5,230] Training sessions of 60 minutes in groups of 8-15 women instructed by a physiotherapist were offered once a week over a period of 12 weeks (between 20 and 36 pregnancy weeks). Each group session consisted of three parts:

1) 30-35 minutes low impact aerobics (no running or jumping). Step length and body rotations were reduced to a minimum, and crossing of legs and sharp and sudden changes of position were avoided. The aerobic dance program was performed at moderate intensity, defined as 12 and 14 on Borg's rating scale of perceived exertion[40] (Appendix 2).

2) 20-25 minutes strength exercises using body weight as resistance, including exercises for the upper and lower limbs, back extensors, deep abdominal muscles and PFM. Three sets of ten repetitions of each exercise were performed. The PFMT was based on the one used by Bø et al.[55] and repeated in the trial by Mørkved et al.[226]

3) 5-10 minutes of light stretching, body awareness, breathing and relaxation exercises.

In addition, women were encouraged to follow a written 45 minute home exercise program at least twice a week (30 minutes endurance training and 15 minutes strength and balance exercises) (Appendix 3).

Women in the control group received standard antenatal care and the customary information given by their midwife or general practitioner. They were not discouraged from exercising on their own. Women in both groups received written recommendations on PFMT, diet and pregnancy related lumbopelvic pain.

Methods

Pre-tests were done at 18-22 weeks and post-tests at 32-36 weeks of pregnancy. The women met at the hospital for assessment. Height and weight were measured by an assessor. Frequency, intensity, duration and type of physical activity including PFMT were recorded for both groups in a questionnaire at inclusion and follow-up. In addition, women in the intervention group registered PFMT in a training diary. Adherence to the protocol was defined as exercising three days per week or more on moderate to high intensity. Performing the exercise program was strongly emphasized and recorded in the women's personal training diary and through reports from the physiotherapists leading the training groups.

Study I – Assessment of GDM

The primary outcomes of the RCT were the prevalence of GDM and insulin resistance estimated by the homeostasis model assessment method (HOMA-IR).[202] HOMA-IR is an empirical mathematical formula based on fasting plasma glucose and fasting plasma insulin levels to calculate insulin resistance [(fasting plasma insulin (µIU/mL) x fasting plasma glucose (mmol/L))/22.5]. All participants underwent a 75 g OGTT at inclusion (18-22 weeks) and at the end of the training period (32-36 weeks). Fasting and 2 hour glucose levels were measured in serum by the routine methods used by the hospital laboratory. GDM was diagnosed according to the WHO criteria as fasting glucose level in fasting whole blood ≥ 6.1 mmol/L or plasma glucose ≥ 7.0 mmol/L, or 2 hour value ≥ 7.8 mmol/l.[11] In addition, secondary outcomes, such as pregnancy complications and outcomes (e.g. newborn weight, gestational age, Apgar scores) were registered from the birth journal.

Study II – Assessment of LPP

Possible effects of regular exercise during pregnancy on LPP were one of six other pre-specified outcomes. LPP and sick leave due to LPP were measured on self-reports. The prevalence estimate of LPP was based on a simple question: "Do you have pain in the pelvic and/or lumbar area?" (Yes/No).

Secondary outcomes were disability, pain intensity and fear-avoidance beliefs. Disability was measured by The Disability Rating Index (DRI) containing 12 questions concerning physical function, of which each question is scored on a 100 mm visual analog scale from "no disability" to "totally unable".[275] The DRI index is calculated as the mean of 12 questions. Since pain intensity varies throughout the day,[209] the women were asked about worst pain in the morning and the evening on Visual Analog Scales (VAS 0-100 mm). The modified Fear-Avoidance Beliefs Questionnaire (mFABQ) consists of four of the five items from the fear-avoidance beliefs about physical activity.[188] Ratings were made on 0 to 6 point scale ranging from strongly disagree to strongly agree. Scores may range from 0 to 24 with high scores showing stronger fear-avoidance beliefs.

Study III – Assessment of incontinence

Possible effects of regular exercise during pregnancy on incontinence were another of the six pre-specified outcomes. UI was measured by self-reports using a severity index.[280,281] Women were asked to report their urinary leakage when A) coughing / sneezing / laughing, B) when being physically active (running or jumping), C) when sudden changes in position / lifting or D) leakage accompanied by a strong urgency to void. Answer alternatives were "Yes" or "No. Urinary leakage was subclassified according to the definitions given in the standardized terminology of lower urinary tract symptoms.[144] Women confirming any type of urinary leakage (alternative A, B, C or D) were referred to as having UI. Women confirming loss of urine in association with alternatives A, B or C were defined as having SUI, while women confirming loss of urine with alternative D were defined as having UUI, The outcome measures of UI were further divided into two severity categories with respect to frequency, "urinary leakage < once per week" or "urinary leakage ≥ once per week (severe UI)".

AI was registered as FI and flatal incontinence during the previous four weeks based on one question from the St. Marks score.[317] Women reporting leakage of solid and/or liquid stool during the last four weeks were categorized as fecal incontinent, and women reporting flatus during the last four weeks were categorized as flatal incontinent.

Study IV – Assessment of energy expenditure

Energy expenditure was measured with SenseWear[TM] Pro$_2$ Armband (BodyMedia Inc., Pittsburgh, PA, USA), an activity monitor including a two-axis accelerometer, a heat flux sensor, a galvanic skin response sensor, a skin temperature sensor and a near-body ambient temperature sensor, which collects minute-by-minute data with up to 14 days memory store. The SenseWear[TM] Pro$_2$ Armband was attached to the right arm over the triceps brachii muscle at the mid-point between the acromion and olecranon processes, in accordance with the manufacturer's instructions (Figure 5A). Data from the monitor were downloaded with software developed by the manufacturer (SenseWear Professional Research Software version 6.1; BodyMedia Inc.).

Oxygen consumption (VO$_2$) was measured using a portable oxygen analyzer with mixing chamber (MetaMax II, CORTEX Biophysik MetaMax® II portable CPX system; Cortex Biophysic, Leipzig, Germany). The analyzer was validated against the Douglas bag technique in five non-pregnant individuals during walking and running on a treadmill. The analyses showed 10–15 % overestimation of oxygen consumption measured by MetaMax II. Calibration was conducted before each test period. Expired gases were collected via a breathing mask (Figure 5B). A gas calibration of the O$_2$ and CO$_2$ analyzers, volume calibration of the volume transducer and calibration of the pressure analyzer were performed before all tests, in accordance with the manufacturer's instructions. Data were analyzed with Metasoft v1.1 (Cortex Biophysic).
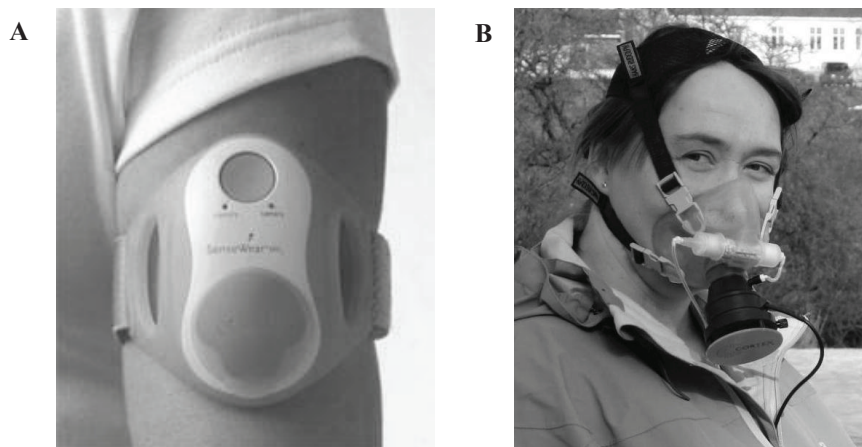
Figure 5. The SenseWear^{TM} Pro$_2$ Armband attached to the right arm (A) and the MetaMax II breathing mask (B).

Both devices were synchronized with a digital clock prior to measurement. The portable oxygen analyzer and the breathing mask were attached to the woman and the measurement started. The measurement period lasted for approximately 90 minutes during daytime, and various physical activities were performed by the participating women. All started with 15 minutes of sedentary behavior, sitting on a chair reading magazines. Thereafter, nine women performed 60 minutes of calisthenics (rhythmic aerobic exercise with stretching, strength and co-ordination exercises to music) in a group setting led by an instructor. They ended their exercise period with 15 minutes cycling on a bicycle ergometer. Another 20 women performed 30 minutes brisk walking outdoors followed by 10 minutes relaxing in a sitting posture, 15 minutes cycling on a bicycle ergometer and then 20 minutes calisthenics, all led by an instructor. The intensity of activities was not limited. The test leader was on site, supervising the activities. The type and estimated length of activities were registered by the test leader during the measurement period. Data from the direct measurements of VO$_2$ and SenseWear^{TM} Pro$_2$ Armband were transferred to Microsoft Excel® and synchronized for further analysis. All data were computed at one minute intervals. The VO$_2$ data were transformed into kilojoules per minute by multiplying VO$_2$ in liters per minute by a factor of 20.15.[203]

Ethics

The procedures followed were in accordance with ethical standards of research and the Helsinki declaration.[309] The women received written (Appendix 4) and oral information, and they signed informed consent forms. The participants were not compensated financially. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 4.2007.81) and registered with Clinical trial gov (NCT 00476567).

Power calculations

Studies I-III

For the principal power calculation of the trial we assumed a GDM prevalence of 9 % in the control group and a prevalence of 4 % in the intervention group (risk difference of 5 %). Under these assumptions a two-sample comparison (Chi squared) with a 5 % level of significance and power of 0.80 gave a study population of 381 patients in each group. This sample size was able to detect a 0.2 SD difference on continuous variables (insulin resistance) given the same power and significance level. Assuming a 10 % dropout rate we needed to include about 880 pregnant women.

Study IV

Sample size calculation was based on a standard deviation of 5 and 7 kJ (per min) with a significance level of 0.05 and power of 0.80. We needed 24 subjects to detect a mean difference of 5 kJ between indirect calorimetry and SenseWear^{TM} Pro$_2$ Armband.

Statistical analyses

Study I

The primary data analysis was according to the "intention–to-treat" principle using Stata software version 10.0 for Windows (Stata Corporation, College Station, Texas). A two sample test of proportions for univariable analyses was used for complete case analysis of continuous variables and a simple linear regression was used for univariable analysis and analysis of covariance when adjusting for baseline values. The estimated risk differences were accompanied with 95 % confidence intervals (CI) and corresponding p-values. A mixed model with random slopes was used to assess the potential impact from missing data. This model used the interaction between the treatment group and time to estimate the baseline adjusted differences between the exercise and control groups. Exploratory analyses using the same statistical models were performed to compare women in the intervention group who adhered to the protocol with the total control group.

Studies II-III

The data were analyzed according to the "intention–to-treat" principle using binary logistic regression for dichotomous variables and ANCOVA for continuous variables. The results were presented as crude and baseline adjusted estimates with 95 % CI. The statistical analyses were performed with SPSS® (Statistical Package for Social Sciences, version 19 for Windows; SPSS Inc., Chicago, USA).

Study IV

A Bland-Altman plot was constructed to demonstrate the relation between the differences (SenseWear^{TM} Pro$_2$ Armband minus indirect calorimetry) and the average values of the two methods for recording energy expenditure during the measurement period. The mean differences and limits of agreement were calculated according to Bland and Altman.[36] A two-way mixed, single-measure, parametric intraclass correlation [ICC (3,1)] was performed for evaluating the extent of agreement between SenseWear^{TM} Pro$_2$ Armband and indirect

calorimetry. Analyses were conducted in SPSS® (Statistical Package for Social Sciences, version 15 for Windows; SPSS Inc., Chicago, USA).

RESULTS

In all, 875 women consented to participate in the trial. Twenty women were excluded or withdrew before the first examination: thirteen did not meet the inclusion criteria, five miscarried and two had twin pregnancies. A total of 855 women were randomly allocated to an intervention group or a control group (Figure 6). However, 33 women in the intervention- and 61 in the control group were lost to follow-up. Data from 396 intervention group women and 365 control group women were included in studies II and III. In addition, 21 intervention group women and 38 control group women failed to complete the OGTT. Data from 375 intervention group women and 327 control group women were included in a complete case analysis in Study I.
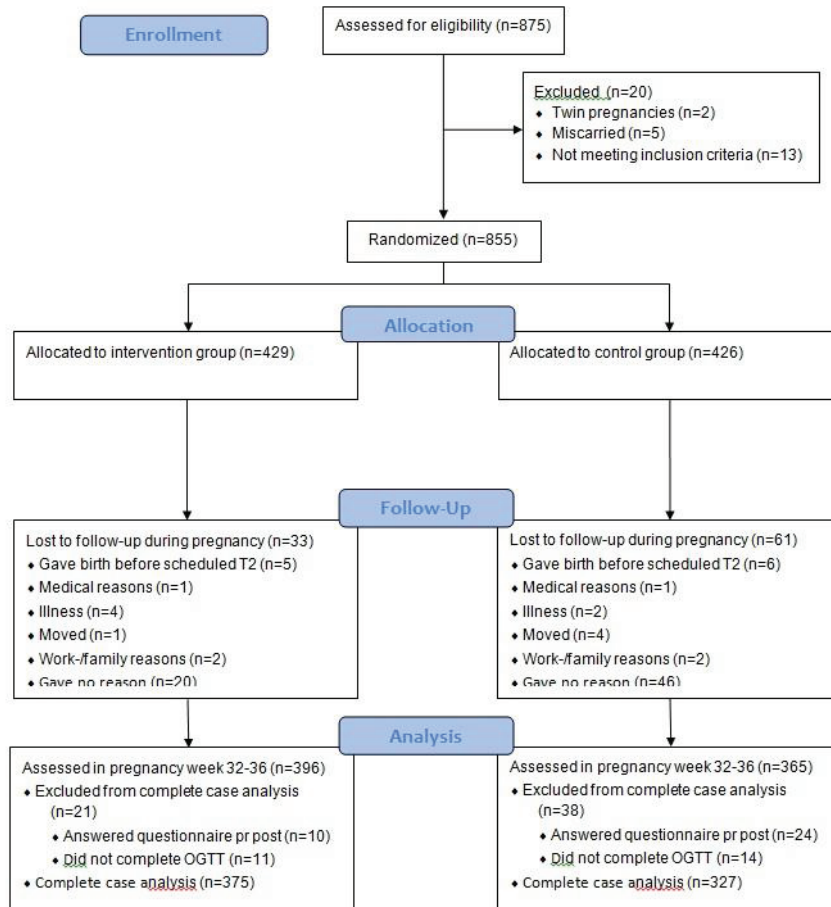

Figure 6. Flow of study participants.

Group characteristics

The groups had similar baseline characteristics (Table 7). Adherence to protocol (exercising three days per week or more at moderate to high intensity) in the intervention group was 55 %. For comparison 10 % in the control group exercised three days per week or more at moderate to high intensity at follow-up (p<0.001). In the intervention group, 72 % exercised at least once per week compared to 30 % in the control group (p<0.001). In the intervention period, women in the intervention group exercised 2.0 (95 % CI 1.9-2. 2) days per week on moderate to high intensity compared to 0.7 (95 % CI 0.6-0.8) in the control group (p<0.001). There was no difference between groups in weight gain, weight and BMI at follow-up (Table 7). No serious adverse events related to physical exercise were seen, and the outcomes of pregnancy were similar in the two groups.

Table 7. Maternal characteristics at baseline and follow-up.

	Intervention group (N = 429)	Control group (N = 426)	p-value
At inclusion (pregnancy week 18-22):			
Age – years	30.5 ± 4.4	30.4 ± 4.3	0.70
Parity			0.71
0	247 (58)	239 (56)	
1	125 (29)	129 (30)	
2+	57 (13)	58 (14)	
Weight – kg	70.4 ± 9.8	70.8 ± 10.3	0.51
BMI – kg/m^2	24.7 ± 3.0	25.0 ± 3.4	0.14
At follow-up (pregnancy week 32-36):			
Weight – kg	77.2 ± 10.0	77.6 ± 10.4	0.60
Weight gain – kg	7.0 ± 2.4	7.2 ± 2.6	0.17
BMI – kg/m^2	27.1 ± 3.1	27.4 ± 3.4	0.15

Data are mean ± standard deviation or n (%).
BMI denotes Body Mass Index.

Main results

The results are described in detail in each of the papers, hence only a summary of the main results is given here.

Study I – GDM

No differences were found in the prevalence of GDM between groups; 25/375 (7 %, 95 % CI 4.3-9.7) intervention group women compared to 18/327 (6 %, 95 % CI 3.3-8.6) control group women (p=0.52). Complete case analysis demonstrated lower fasting insulin and insulin resistance in the intervention group compared to the control group at follow-up, but when adjusting for baseline values the differences were reduced. To evaluate the potential effects of attrition and missing data, a linear mixed effects model was applied for all included subjects, N=855. The results were similar (lower fasting insulin and insulin resistance in the intervention group), but the differences were halved when adjusting for baseline values.

Study II – LPP

There were no differences in the percentage of women reporting LPP in the two groups after the 12 weeks intervention period. However, the proportion of women on sick leave due to LPP and the odds ratio (OR) were lower in the intervention group (p=0.01). When adjusting for baseline sick leave due to LPP, the estimated OR was still significantly lower (p=0.04). No differences were found between groups regarding disability, pain intensity or fear-avoidance beliefs both unadjusted and adjusted for baseline values of the outcome measure.

Study III – Incontinence

After the intervention period, significantly less women in the intervention group reported UI and SUI. The findings were consistent when adjusting for baseline values. A lower proportion of women in the intervention group (3 %) than the control group (5 %) reported FI, however, the difference was not statistically significant.

Subgroup analyses were done based on groups stratified according to urinary continence status at inclusion. Sixty-nine percent of the continent women and 40 % of the incontinent women were nulliparous. The subgroup analyses showed that women in the intervention group who were continent for urine at inclusion, reported significantly less severe SUI ($\geq$once per week) and UUI (p=0.03 and p=0.006) after the intervention period. Furthermore, among women who were incontinent for urine at inclusion, the proportion reporting UI, UI $\geq$once per week and SUI after the intervention period was lowest in the intervention group (p=0.002, p=0.03 and p=0.007). The findings were consistent when adjusting for baseline values. Subgroup analyses on groups stratified according to anal continence status at inclusion showed no significant difference.

In the intervention group, 95 % reported weekly PFMT at 32-36 weeks of gestation compared to 79 % in the control group (p<0.001). The proportion of intervention group women performing PFMT three times per week or more was 67 % compared to 40 % in the control group (p<0.01).

Study IV – Energy expenditure
A total of 29 women were included in the validation study. Thirteen women were in the second trimester and 16 in the third trimester. Twenty women carried out conditioning exercises such as brisk walking, running or bicycling in addition to strength exercises, whereas nine participated in calisthenics and rhythmic aerobic exercise. The mean period with energy expenditure recordings was 85 minutes (range 80–89).

Mean total energy expenditure during the period with free-living activities was 1,618 kJ (95 % CI 1,492–1,744) for indirect calorimetry and 1,482 kJ (95 % CI 1,364–1,600) for SenseWear^{TM} Pro$_2$ Armband. When comparing energy expenditure during free-living activities, the mean difference and limit of agreement from the Bland–Altman plot was −136 ± 343 kJ. SenseWear^{TM} Pro$_2$ Armband underestimated energy expenditure by 9 %.

DISCUSSION

The central aspects in each of the studies have been discussed in the respective papers. Here I will concentrate on some methodological aspects and address the main issues across the studies.

To my knowledge this is the largest RCT assessing exercise during pregnancy in the prevention and treatment of pregnancy-related conditions. Healthy pregnant women were included. Women in the intervention group were offered a 12-week exercise program, including PFMT, to be performed three times per week in the second half of pregnancy. A total of 55 % of intervention group women exercised three times per week in late pregnancy, compared to 10 % in the control group. At follow-up, there was no difference between groups in the prevalence of GDM or level of insulin resistance. The prevalence of LPP in both groups was similar, however, less women in the intervention group were on sick leave due to LPP. The intervention group reported less UI in late gestation, and this group had both a primary and secondary prevention effect. A physical activity monitor was validated and found to be a valid instrument in pregnant women. The TRIP trial was a two-armed, two-centered randomized controlled trial with concealed randomization. However, there are some limitations.

Methodological aspects

Design
RCT is considered to be the gold standard design when assessing the effects of treatment, providing the most reliable evidence on the efficacy of healthcare interventions.[217] Proper randomization reduces selection bias at trial entry, balancing both known and unknown factors. The intervention group was offered a regular exercise program. The control group women received no intervention, but were not advised against exercising on their own. The optimal study design would be to have a control group free from exercise. However, it would be unethical to stop control group women exercising on their own, and adding a control group

of sedentary pregnant women would ruin the randomized design. Including only sedentary women with no previous habit of regular exercise in the trial would have been another option.

Blinding is considered an important methodological factor to ensure high internal validity of a RCT. In the TRIP trial the investigator was aware of group allocation. Addition of a blinded assessor would increase the costs and thus was difficult for practical reasons. However, analysis of blood glucose and insulin was done blinded to group allocation, and prevalence of LPP and incontinence were based on self-reports minimizing the effect of bias due to the non-blinded study design.

The possibility of recall bias is minimal in the TRIP trial, since women were asked to report LPP and incontinence at present, except for AI in which women were asked to recall symptoms last four weeks.

It is possible that women in the intervention group were «eager to please» because they were offered a free exercise class. Thus, they may have reported fewer symptoms than they actually experienced. On the other hand, the exercise program exposed women attending the intervention group to a variety of situations that trigger incontinence and challenges the local and global spinal stabilizing muscles. This means that the effects of the training program may be underestimated regarding incontinence and LPP.

Study population

Another limitation to be considered is selection bias. Less than 10 % of all women attending a routine ultrasound scan in the study period assigned for the trial (875/12,000). To be able to attend, women should be Caucasian, healthy with low risk pregnancies and live within 30 minutes drive from the hospital. The actual number of women meeting the inclusion criteria is not known. The women volunteering for the trial contacted the project coordinator after receiving a written invitation, and were mainly well motivated to exercise during pregnancy. Women in the TRIP trial might therefore be a selected group of women already in good physical condition.

Women included in the TRIP trial were from an urban area in Norway. When compared with a general population of pregnant women in Trondheim, women in the MoBa study and the Medical Birth Registry, the external validity was found to be acceptable for Norwegian pregnant women regarding age, parity, BMI, exercising habits, gestational age at birth and birth weight (Table 5 and 6). However, in the MoBa study the youngest women (<25 years), those living alone, mothers with >2 previous births, previous stillbirths and smokers were strongly under-represented compared with the total population pregnant women in Norway in the same time period.[232]

The intervention was based on both group training and individual training. This may have caused practical difficulties for some of the invited women (childcare, work, transport). We have not been able to assess the characteristics of non-participants. However, women in the TRIP trial were healthy Caucasian women with mean BMI within the normal range. Therefore, the results from our trial should be interpreted with caution in groups with less physical activity, higher BMI and other ethnicities.

Intervention

The intervention was based on the current recommendations for the general population (exercising three times per week including both aerobic and strength training). Healthy pregnant women are encouraged to follow the same exercise recommendations as non-pregnant. The exercise program required no equipment, all strength exercises were performed with own body weight as resistance. The women chose according to their own preferences what type of endurance training to perform when doing the home exercise program. The strength and balance exercises were similar to those performed in the group sessions. All strength exercises were shown in three different positions reflecting various degrees of difficulty. The weekly group sessions were led by skilled physiotherapists, who followed a standardized exercise program. Supervision of exercises is critically important in improving quality of exercise performance. The supervision by a qualified professional and proper prescription of the program variables have been found to be important for effective resistance training.[175] In addition, a strong correlation between the quality of exercise performance and decrease in pain in non-pregnant patients with neck pain and LBP has been found.[112] The exercise program also included information on related topics such as incontinence, LPP,

ergonomics, exercise in pregnancy and the postpartum period. Most of the exercise groups were visited by a gynecologist who informed about exercise in pregnancy, contractions, and answered questions from the women.

The control group received standard care and written information about LPP, PFMT and diet. The brochure on PFMT included a detailed evidence-based PFMT program similar to the PFMT program included in the intervention. A high percentage of women in the control group reported performing PFMT. In spite of this, the intervention group demonstrated significantly less UI than the control group women. However, women in the control group were not instructed in correct VPFMC at enrolment in the trial. Since it is well known that many women do not perform a VPFMC correctly after only verbal or written information,[46,56] there is a possibility that some women in the control group performed the contractions incorrectly. Other important issues are thorough instructions and motivation. Women in the intervention group had weekly instructions and practical training in groups led by skilled physiotherapists.

The two examinations during the study period were done at the hospital, and all women diagnosed with GDM were referred to standard follow-up of diabetes nurses and endocrinologists. If other problems were discovered, women were referred to a midwife or gynecologist. Both examinations were in addition to standard antenatal care.

The 12-week intervention period was during the second half of pregnancy. There were several reasons for this approach. First, the study invitation was attached to an invitation to a routine ultrasound scan. Thus, we were able to invite all eligible pregnant women in the catchment areas. Second, all women had ultrasound before inclusion, and we were assured that only women with one single fetus and a low risk pregnancy were included. And third, at study start there were some discussions between experts regarding leisure time physical activity and the risk of early miscarriage.[197] However, in the light of our findings and previous research, I believe that promoting health of women of reproductive age before conception and helping women to have a healthy and active lifestyle during pregnancy are the most promising approaches in preventing pregnancy-related conditions such as GDM, LPP and incontinence.

Compliance

Compliance is essential for proper interpretation of the effect of an exercise intervention. In this trial only 55 % managed to follow the exercise protocol. Reported reasons for not following the protocol were mostly attributable to pregnancy symptoms, child care and work commitments. Exercising three times per week can be hard to achieve for a pregnant women taking into account family- and work commitments and a body in continuous change. Two-thirds of the exercise protocol was exercises to be performed home. From a public health perspective strategies to increase adherence to exercise must be of importance. This might be through public health information campaigns, information about health benefits of regular exercise given by a physiotherapist during antenatal care, offering free exercise courses during pregnancy and that the employer offers time for exercise included in working hours. It is important to emphasize that health benefits of regular exercise is not only limited to maternal profits, but is most likely to influence the fetus and protect against overweight, metabolic syndrome, diabetes and other cardiovascular diseases in the adolescents and adulthood.

Withdrawals and loss to follow-up

Loss to follow-up after recruitment and attrition affects the generalizability of the results. Any loss to follow-up decreases internal validity, but differential rates of loss to follow-up among comparison groups cause major damage.[285] In general, less than 5 % loss to follow-up in RCT is acceptable, whereas greater than 20 % loss to follow-up will potentially imply serious threats to validity.[285] In the TRIP trial we experienced 11 % loss to follow-up on self-reported outcomes and 18 % on OGTT. The respective percentages in intervention and control groups were 8 % vs. 14 % on self-reports and 13 % vs. 23 % on OGTT. These differences were considered acceptable. One reason for loss of data at the OGTT was that performing the OGTT caused nausea in some women who therefore did not complete the test. In addition, the tests were performed in daytime due to the need of an overnight fast, and lasted for almost three hours including OGTT, questionnaires and physical tests. This may have been difficult for some women due to work commitments.

Statistics and power calculations

All participants were included in the analysis in the groups to which they were originally assigned ("intention-to-treat" analysis). The intention-to-treat principle underlies the primary analysis in an RCT to avoid bias associated with non-random loss of participants.[181] Since only 55 % adhered to the exercise protocol it is difficult to conclude on the direct effect of the exercise protocol on glucose metabolism, LPP and incontinence. Explorative analysis can be performed on the protocol adherents. However, such analysis has some limitations since they are based on only a subset of the subjects initially included in the trial. The results may be explained by other confounding variables and results should therefore be interpreted with caution.

When the present trial was planned no prevalence studies on GDM from Norway were published. The power calculation of the trial was based on previous international studies reporting prevalence up to 14 %. Since the TRIP trial was a population-based approach and invited all women irrespective of risk factors, a prevalence of 9 % was chosen and a reduction to 4 % in the intervention group was assumed. The overall GDM prevalence in the TRIP trial was 6.1 % at 32-36 weeks of pregnancy indicating that the study was slightly underpowered. However, even with a larger trial, there would probably be no statistically significant difference in GDM prevalence between groups (7 % vs. 6 % in the present trial). This is supported by our secondary outcome, 120 minutes OGTT, which was not different between the groups. Being a continuous variable, this outcome has considerably more power. With a sample size of 440 in each arm, we had a power of 87 % to detect a difference in 120 minutes OGTT of 0.25 mmol/L based on a t-test for two independent samples given a common SD of 1.2 in the groups and a 2-tailed alpha of 0.050.

The prevalence of AI in late pregnancy was found to be 5 % vs. 3 % in the present trial. AI is less prevalent during pregnancy than UI, and the trial was underpowered to demonstrate any possibly difference between groups as shown by the wide confidence intervals.

Despite the randomized design some of the baseline characteristics were significantly different between groups at inclusion. This was accounted for in the statistical analysis.

Outcome measurements

Physical activity and exercise

Physical activity is a complex action characterized of its intensity, duration, frequency and type of activity.[218] The level of physical activity in the TRIP trial was assessed with self-reports which have some limitations. The questions regarding exercise (frequency, intensity and duration) were taken from the Pregnancy Physical Activity Questionnaire (PPAQ). Intensity is found to be the least valid component assessed by questionnaires.[276] It has been shown that much of a women's moderate-intensity activity is performed in unstructured settings, and that activities are performed for short periods and are intermixed with light-, moderate-, and sometimes vigorous-intensity activities.[201] The challenge with self-reports is to capture all type of activities. In general, adults are recommended to engage in regular exercise and increase the level of daily physical activity (Figure 7). It might be that not only the amount of weekly exercise, but the levels of daily energy expenditure (related to the women's occupation, housework, child and family care, leisure activities and exercise) in sum are the most important aspects for disease prevention. A physical activity monitor would provide a more objective answer to the weekly level of exercise and daily total energy expenditure. However, the physical activity monitor needs to be validated for the actual population studied. The SenseWear^{TM} Pro$_2$ Armband was found to be a valid objective physical activity monitor, but due to lack of time and resources we were not able to use this device on all women in the TRIP trial.
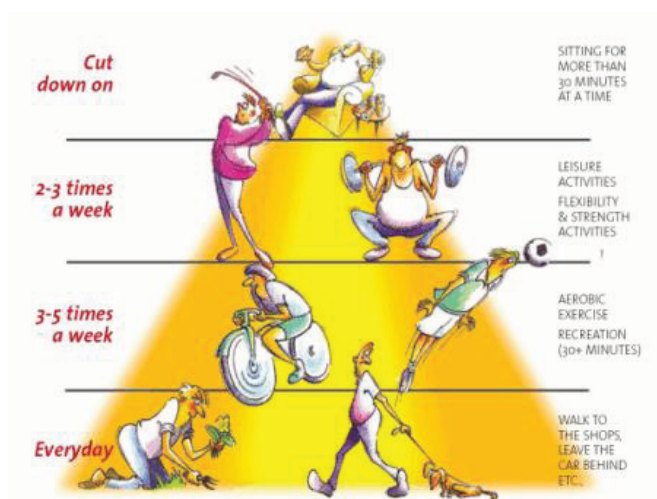

Figure 7. The physical activity pyramid (http://irishcancer.ie/prevention/physically_active.php)

Gestational diabetes

Fasting and 2-hour glucose levels were measured in serum by the routine methods used by the hospital laboratory the same day as taken. The level of insulin was measured in serum after being stored in a freezer (-80 °C). GDM was diagnosed according to the WHO criteria (fasting glucose level in fasting whole blood ≥6.1 mmol/L, or plasma glucose ≥7.0 mmol/L, or 2-hour value ≥7.8 mmol/L).[11] Comparison between different studies can be difficult because the OGTT procedure and diagnostic criteria vary.[70] We chose to use HOMA-IR as a measure of insulin sensitivity, but HOMA-IR may not be the most sensitive way of assessing the impact of exercise on insulin resistance. HOMA-IR is regarded as a good measure of overall insulin resistance in pregnancy, but it may provide a better reflection of liver rather than peripheral insulin resistance.[169] Exercise most likely exerts its effect peripherally by reducing peripheral muscle insulin resistance.[59]

Lumbopelvic pain

The prevalence estimate of LPP was based on self-reports, and was not verified with clinical tests. Some authors argue that it is important to distinguish between LBP and PGP,[326] but this was not done because it was not within the scope of this thesis to classify pain into different types, or according to location. It has been argued that because back pain is a subjective phenomenon, self-report is the most appropriate method of measuring this outcome.[173] However, different definitions of back pain may result in different estimates of prevalence and incidence, and no single definition has been generally accepted in back pain research, making comparison between studies difficult. We did not ask the women whether they had LPP before the present pregnancy or if the onset of pain were during the present pregnancy. Thus, we do not know if we were dealing with old recurrent pain or a new pain. Östgaard et al.[348] have shown that more than one in five (22 %) women had ongoing back pain before getting pregnant. We assume that this may be true for a number of women included in the TRIP trial, and this was another reason why the term "pregnancy-related" was not used together with "lumbopelvic pain".

The DRI reflects function and disability rather than pain. It was primarily developed for non-pregnant with LBP, but has been used on a wide range of musculoskeletal problems. DRI surveys the difficulties in performing specific activities. Hence it is the degree of difficulty

that is assessed. The DRI is not optimal for pregnant women since activities such as "lifting heavy objects" and "running" are included. When the TRIP trial was initiated, no pregnancy-related instrument for physical ability was found. Later, the Pregnancy Mobility Index[321] and the pelvic girdle questionnaire[297] were developed. The Pregnancy Mobility Index[321] evaluates functioning in relation to back and pelvic pain in the following three main areas: daily mobility in the house, household activities and mobility outdoors. The pelvic girdle questionnaire[297] is a condition-specific instrument for assessing activity limitations in women with PGP during pregnancy and postpartum.

Pain is multidimensional and the respondents communicate far more than just intensity about their pain.[339] The reliability and validity of measuring pain intensity by VAS have been discussed.[303] Pain intensity measured by VAS is a subjective phenomenon quantifying the pain. The repeatability of VAS has been found to be good.[339] The VAS used for rating pain intensity in LBP showed good reliability over 24 hours,[265] and the VAS also showed sufficient reliability when used in acute pain.[32] A number of studies have demonstrated that pathology does not correlate well with pain, importantly, the absence of identifiable pathology does not mean the absence of pain.[339]

Fear-avoidance refers to the avoidance of specific movements or activities based on fear of pain or (re)injury. The mFABQ is a modified version of the original FABQ, and consists of four of the originally five questions regarding general physical activity. The mFABQ was chosen since it is found that even subjects without pain can answer these questions.[188]

Both DRI and VAS are continuous variables and intend to provide more graded information on LPP than merely the presence or absence of LPP. The DRI and VAS has previously been used in pregnant and postpartum women assessing LPP,[228,240,269,299] thus allows for comparison between studies which is considered important. This was the main reason for choosing DRI and VAS as outcome measures.

Incontinence
Both UI and AI were measured by self-reports. The severity index[280,281] and the St. Marks score[317] are validated and reflect the frequency and amount of leakage and have been used in

numerous studies in different populations. The question of UI is in accordance with the International continence society's present definition of UI symptoms; "any complaint of involuntary leakage of urine".[144] In the TRIP trial we wanted to cause minimal discomfort to healthy pregnant women and therefore did not perform any quantification of the amount of urine lost with standardized bladder volume. However, Haylen et al.[144] emphasize that to diagnose "urodynamic stress incontinence" the correlation between a woman's symptom, sign, and urodynamic investigations should be included

The relationship among different severity measures of UI in women with predominantly SUI has been found to be weak to moderate, and they appear to measure different aspects of the incontinence condition.[12] Thus, the different severity measures are not interchangeable when characterizing a patient population or assessing outcomes. To facilitate comparison between studies a standardized measurement tool should be agreed upon.

AI was measured with the St. Marks score which covers frequency, severity, urgency, pad use and social restrictions.[317] The St. Marks score is a widely used severity score, ranging from 0 (complete continence) to 24 (complete incontinence). In the TRIP trial only the first question regarding frequency was used ("have you experienced leakage of solid stool / liquid stool / gas last four weeks"). Women answering rarely / sometimes / weekly / daily were categorized as having AI.

AI during pregnancy is less prevalent than UI and therefore prone to type II error, i.e. the trial was too small to detect any possible clinical differences between groups.

Both the severity index and the St. Marks score are validated and reliable measurement tools widely used in previous research, and therefore chosen for this trial.

Main results

Study I – GDM

No previous RCT's have assessed the effect of regular exercise in the prevention of GDM in a general population of pregnant women. However, two smaller trials have assessed the effect on insulin resistance.[23,151] The present results on insulin resistance are in accordance with the results from Hopkins et al.[151] Adherence to the exercise protocol in the TRIP trial was 55 % vs. 75 % in the trial by Hopkins et al.[151] Both trials included women with low risk of GDM, the interventions lasted for 12 weeks and started mid-pregnancy. In contrast, Barakat et al.[23] included pregnant women at 6-9 weeks of gestation and women were encouraged to exercise three times per week throughout pregnancy. The adherence to the exercise protocol was 85 %. In gestational week 24-28 the glucose levels were lower in the intervention group compared to the control group. However, that trial had some limitations; glucose levels at baseline were not measured, the glucose screening test was done non-fasting and there was no control of the level of physical activity in the control group. Clapp et al.[73] assessed whether increasing or decreasing levels of exercise mid-pregnancy altered fetal growth. The results suggested that fetoplacental adaptations are dependent on the period of gestation in which exercise training is initiated and maintained, as well as the intensity or volume of exercise performed.[73]

A small study of five healthy nulliparous women, who underwent a 100 g OGTT 30 min following a 30 min exercise bout on 50 % of maximal aerobic capacity in the third trimester, and a similar OGTT on a day without prior exercise, found no differences in the plasma glucose response between the control and exercise conditions. Plasma insulin levels were lower after exercise (23 % lower, $p<0.05$) indicating an increase in peripheral insulin sensitivity.[344]

In non-pregnant women, the acute effect of exercise includes increased glucose uptake in skeletal muscle via an insulin-independent mechanism that bypasses the insulin signaling defects associated with insulin resistance.[140] The effects of one single exercise session on insulin sensitivity persist up to 48 hours. Individuals who undertake regular training, may change the expression or activity of a variety of signaling proteins involved in the regulation of skeletal muscle glucose uptake,[347] and pre-pregnancy physical activity has been

consistently associated with a reduced risk of GDM.[313] Oken et al.[239] found that vigorous physical activity before pregnancy and continuation of activity into early pregnancy may reduce a woman's risk for developing abnormal glucose tolerance and GDM. During pregnancy, an increase in insulin resistance occurs secondary to the diabetogenic effect of one or more of the gestational hormones secreted by the placenta.[17] The marked reduction in maternal insulin sensitivity in late pregnancy increases the glucose supply to the fetus.[61] The results from Hopkins et al.,[151] Barakat et al.,[23] and the TRIP trial suggest that in a normal healthy pregnancy, maternal insulin sensitivity is regulated persistently to achieve optimal fetal growth and is not sensitive to the chronic training adaptations in late pregnancy as previously described in non-pregnant individuals.[152] The findings support the safety of maternal exercise for fetal well-being. Thus, there is a possibility that regular exercise before pregnancy and in early pregnancy is more important than exercise during the second half of pregnancy, since chronic changes in the regulation of skeletal muscle glucose uptake are adapted, and women may be better to handle the metabolic stress of a pregnancy.

In the literature there is agreement that exercise must be undertaken regularly to have beneficial effect, but there is conflicting evidence whether the intensity or volume of exercise is the most important determinant for improvement of insulin action in the non-pregnant.[139] In addition, there are unanswered questions regarding gestational endocrine changes and glucose homeostasis in general, and insulin-stimulated glucose uptake in particular. It is well known that exercise has an important role both in the prevention and treatment of T2DM. Even though T2DM and GDM seem to have overlapping causes, it might be that other mechanisms influence glucose metabolism in GDM than in T2DM. Since only 55 % of the intervention group women adhered strictly to the exercise protocol, we cannot conclude if exercising at least three times per week may influence glucose metabolism. If exercise training has an effect on improving peripheral insulin sensitivity in pregnant women, the differences between groups in levels of exercise may have been too small to show any differences. In addition, the intensity of the exercise program was instructed to be moderate (12-14 on Borg's scale) according to the recommendations.[5] Intensity of activity may have been too low. There is some indication that vigorous-intensity activities may have greater benefit for reducing cardiovascular disease and premature mortality than moderate-intensity physical activity.[137]

Controversy still exists about the screening and diagnosis of GDM. In the majority of GDM-cases, carbohydrate intolerance is asymptomatic and can only be detected by routine screening challenge tests. The prevalence of GDM among women without risk factors is low. In the Medical Birth Registry of Norway, 1.3 % of all pregnancies in 2009 were diagnosed with GDM.[307] In a Scandinavian population in Oslo in 2002-2008, the STORK study, a prevalence of 5.6 % was found, and in the TRIP trial 6.1 % was diagnosed with GDM. In the TRIP trial 10 % of the population had a pre-pregnancy BMI >27 kg/m^2 which according to current guidelines in Norway is one criteria of screening for GDM. It is questionable whether the selective screening procedure in Norway captures all women with GDM.

Study II – LPP

The result on reduced need of sick leave due to LPP in the intervention group was in accordance with three previous trials.[120,164,234,350] The intervention in the TRIP trial was from a public health perspective; including women from a general population rather than women with LPP. In Norway, 59 % of pregnant women are on sick leave at least once during pregnancy with an average of 21.5 days off from work,[223] and LPP accounts for the majority of sick leave among pregnant women.[121,223,305,350] Sick leave represents considerable implications for public health costs and productivity. In 1999, SINTEF Unimed reported that each day on sick leave on average constitutes NOK 1700 in costs for the employer.[146] Days on sick leave were not counted in the TRIP trial, but it is likely that total days on sick leave were lower in the intervention group, because of the lower percentage on sick leave (22 % vs. 31 %). Myklebø and Thune reported that the number of pregnant women on sick leave increases with increasing gestation,[223] and Myklebø reported that several healthy pregnant women are sick listed because the work is too demanding or exhausting.[222]

An interesting question is whether the difference in sick leave in the TRIP trial was caused by more frequent exercise in the intervention group or simply by closer follow-up. Being physically active maintain or improve fitness,[208] and a recent RCT has shown that exercising women had an increased perception of health status.[25] In the TRIP trial skilled physiotherapists with knowledge about pregnancy and exercise during pregnancy were leading the exercise groups. In addition, intervention group women knew that they would be referred to a midwife or a gynecologist if adverse pregnancy-related conditions occurred. In a

qualitative study of 19 Australian women, receiving advice regarding exercise from health professionals and receiving reassurance that their pregnancy progressed satisfactorily were two of the motivating factors that facilitated women's engagement in physical activity.[72] The weekly group training was also an opportunity to get social support by other pregnant women. Being with other pregnant women is found to be another motivating factor for physical activity during pregnancy.[72]

The TRIP trial included 855 healthy pregnant women and less than 10 % of the eligible women signed up for the trial. It is possible that women with pronounced early onset LPP did not sign up for this study. However, nearly 60 % of the participants reported experiencing LPP at the time of inclusion, though mildly affected. The generalizability of the study results may not be extended to women with severe LPP. No differentiation between LBP and PGP was done in this study, and we are therefore not able to conclude whether the results on sick leave are representative for women with PGP or LBP only.

To our knowledge only one RCT has studied the preventive effect of exercise on LPP. The trial found a reduction of LPP in the intervention group, but no difference in sick leave due to LPP.[228] That study included only nulliparous women, and the intervention was less intensive with PFMT as main focus. The intervention program in the TRIP trial focused on general fitness and strength. It was designed for pregnant women, but not specifically for women with severe LPP. The weekly group training sessions had only few possibilities of individual adjustments. Research has found that exercise focusing on activation of deep local muscles promoting motor control and stability is superior to general strength exercises in women with PGP.[298,299] In addition, individualization of the treatment is found necessary.[298,299] At inclusion 60 % reported LPP. However, the TRIP trial was not a treatment trial. If the aim of the trial had been to treat LPP the intervention program would have been different. Despite the importance of motor control, muscular strength is still considered a fundamental physical element necessary for health, functional ability, and enhanced quality of life.[174] No women with LPP, regardless of group allocation, received treatment of the physiotherapists involved in the trial, but were advised to contact a physiotherapist and/or their general practitioner.

Study III – Incontinence

Previous trials have documented the effect of intensive PFMT during pregnancy in prevention and treatment of UI,[92,119,171,226,262,279,282] but the TRIP trial is the first to document a prevention and treatment effect of PFMT when implemented in a general exercise program for pregnant women. The role of PFMT in prevention and treatment of AI in pregnancy has been sparsely studied, and one Cochrane review strongly recommends that all future trials on PFMT in antenatal and postnatal women collect data on AI.[141] The TRIP trial was unfortunately underpowered to detect any possible differences in AI between groups. Nevertheless, the TRIP trial is the largest RCT at present assessing prevention and treatment of AI.

General strength training programs for all striated muscles demonstrate an increase in strength due to neurological and morphological factors.[111] The present trial did neither assess strength nor neurological changes after PFMT. In a previous trial including nulliparous women, Mørkved et al.[226] found reduced prevalence of UI and increased PFM strength in the intervention group following a 12 week PFMT program. Studies have found that an increase in strength is found after few weeks of strength training, and the increase in strength continues at least 12 months after starting strength training.[111] The rapid rise in strength at the start of a training program is primarily due to neurological adaptations such as increased motor-unit recruitment and firing frequency.[111] In MRI-studies an increase in muscle thickness is found after 8-12 weeks, with a plateau after 6 months.[111] During pregnancy the continence mechanism is continuously challenged due to the increased weight of the fetoplacental unit. In addition, the TRIP trial included both nulli- and multipara women. Multipara women may have damage to the pelvic floor from previous births. If the intervention period in the TRIP trial had been prolonged, muscle hypertrophy would in theory increase and the prevalence of UI in the intervention group may have been further reduced.

The PFMT followed standard strength training principles and should be performed three days per week. However, in some rehabilitation situations maximum contraction, or overload, is not possible and more frequent training sessions need to be used and are often more desirable.[93] Women in the intervention group with existing UI were therefore encouraged to perform PFMT more frequently than three days per week, most preferable daily.

In spite of the favorable result from previous trials in preventing and treating UI during pregnancy, one study[198] casts doubt on whether the success rate reported in previous trials can be achieved in the "real world". Mason et al.[198] examined the instruction in PFMT given to women during pregnancy or following delivery, to assess the quality of any instruction provided, and to consider these in the light of the women's view of the service. They found that the routine instructions in PFMT during pregnancy or following childbirth were provided on an ad hoc basis. They concluded that there is need for the service to be reorganized so that all women receive high-quality instruction during pregnancy, with a reminder to exercise following birth. It has also been suggested that in order to maximize compliance with PFMT, it may be advisable to concentrate on providing women with more information about UI and developing techniques that help women to remember to perform exercises.[95] Another trial by Mason et al.[199] aimed to investigate whether women who experienced UI following childbirth were provided with information on the condition or whether they seek help and what help they received. The majority (69 %) had not received any information about UI either during pregnancy or following birth. Most women thought that information about UI should be provided during pregnancy to be warned that the condition could occur at this time and following birth.

Comparison of prevalence estimates between studies is difficult because of methodological aspects. However, the trial by Mørkved et al.[226] was performed in the same geographical area 10 years ago and classified women with or without UI with the same outcome measures and at the same gestational age as the TRIP trial. The prevalence of UI was halved in the TRIP trial compared to the previous trial. In recent years following the trial by Mørkved et al.[226] there has been an increased awareness on PFMT both among health professionals and pregnant women which may have resulted in lower prevalence of UI among pregnant women. The studies from Mason et al.[198,199] were performed more than 10 years ago, and the awareness of PFMT may have changed.

A large proportion of women in the control group reported doing regular PFMT during the intervention period. Still, the intervention group demonstrated significantly less UI in late pregnancy. This underscores that for PFMT to be effective, thorough instruction in VPFMC, intensive PFMT and close follow-up is necessary.

Women being physically active are more frequently exposed to higher and more repetitive increases in abdominal pressure compared to more sedentary women. The prevalence of SUI in young nulliparous elite athletes is high,[52,236] and morphologic and functional differences in elite athletes has been found.[179] A myth still persists among birth attendants that strong PFM may obstruct labor. In contrast, Salvesen and Mørkved found that women following a PFMT program during pregnancy reduced the length of the second stage of labor significantly compared to a control group,[278] and other studies have found no negative effect of PFMT on labor.[6,53]

General discussion

The current guidelines

There is international consensus about the importance of exercise during pregnancy, and guidelines for exercise during pregnancy and the postpartum period are worked out by the ACOG,[5] the Society of Obstetricians and Gyaecologists of Canada Clinical Practice Obstetrics Committee and Canadian Society for Exercise Physiology Board of Directors,[83] Sports Medicine Australia,[293] The Royal College of Obstetricians and Gynaecologists,[308] and the Norwegian National Council on Nutrition and Physical Activity.[230] The ACOG states that "In the absence of either medical or obstetric complications, 30 minutes or more of moderate exercise a day on most, if not all, days of the week is recommended for pregnant women."[5]

The ACOG guidelines were based on the recommendations for adults presented in 1995.[247] In 2007, the ACSM and the American Heart Association issued an updated version of the 1995 recommendations on physical activity in the adult population with the intent to provide a more comprehensive and explicit public health recommendation for adults based upon available evidence of the health benefits of physical activity.[137] The recommendations included both aerobic and strength training.[137]

Since ACOG's latest version in 2002 new science has emerged that has enhanced our understanding of the amount of physical-activity expenditure needed and the intensity of exercise needed to improve health outcomes and quality of life in adults, and this has been

taken into account in the new recommendations for adults.[137] Today, pregnant women are recommended to exercise with moderate intensity, and an upper level of safe exercise intensity has not been established. Salvesen et al.[277] found that exercise at intensity above 90 % of maximal maternal heart rate in pregnant elite athletes may compromise fetal wellbeing.

It is now almost a decade since the new guidelines on exercise during pregnancy were published, and in this period an increasing amount of evidence has been published suggesting that the recommendations are too conservative. However, the optimal dose of recreational physical activity (i.e. total volume of energy expenditure and specific frequency, duration and intensity) for pregnant women remains to be determined.[68]

There are only few RCT's assessing the role of exercise in pregnancy, and those published have involved small numbers of predominantly lean, physically active participants. Furthermore, most of the studies have provided minimal quantification of exercise performance.[176] Future trials should aim at including sedentary and/or overweight women. The determination of the optimal dose of physical activity for pregnant women has been hampered by the complexity of assessing physical activity in general. Valid and reliable measurements of activity are critical to understand the influence of physical activity on pregnancy-related outcomes. Today, several physical activity monitors are available and will provide further knowledge about exercise in pregnancy. However, it is of importance that the validity of activity monitors need to be carefully examined in the actual research population.[330] It is unknown whether a dose-response or a threshold of physical activity in pregnancy exists, which would be of major importance for public health policy.[68]

Barakat et al.[24] found that supervised, light intensity resistance exercise training performed during the second and third trimester of pregnancy does not have a negative impact on the newborn's body size. There is evidence that improved muscular strength has beneficial effects in the prevention of chronic diseases as well as in the ability to cope with daily living activities in both healthy and diseased people.[300,341] Other potential benefits of resistance training include better posture and independence. The British[308] and Australian guidelines[293] on exercise during pregnancy include strength training in accordance with the exercise recommendations for adults. Zavorsky and Longo[345] have recently highlighted that there is a need for an updated version of the exercise guidelines in pregnancy into a more concise

format for pregnant women and health professionals. They suggest that specific definition of moderate-intensity exercise or the recommended amount of weekly physical-activity energy expenditure together with light strength training should be included in the guidelines.[345]

Exercise training in antenatal care

Exercise during pregnancy is recommended for healthy pregnant women, but exercise classes are not included in standard antenatal care. It is important that the interventions found effective in RCT's with high methodological quality, are implemented in the ante- and postnatal health care system. The TRIP trial aimed to assess the effect of the recommended levels of exercise. Even though the TRIP trial failed to prove any preventive effect on GDM, the result on reduced sick leave due to LPP and less UI are important findings. In addition, no serious adverse events related to exercise were seen. Providing accurate information and encouraging pregnant women to engage in healthy behavior during pregnancy is a necessary first step toward improving maternal and child care.[60] Each pregnancy is a unique opportunity to educate. Offering women high standard antenatal classes led by skilled physiotherapists should be given priority. In Norway antenatal care is free of charge, and offering exercise classes as part of standard care would eliminate any differences for all social groups. Providing physical activity information to all pregnant women can help reduce disparities in physical activity knowledge and may increase positive attitudes towards physical activity.[60]

During pregnancy and after delivery significant changes take place in the body. Studies have shown that many women experience ill health following pregnancy and childbirth. According to Glazener et al.[116], as many as 17 of 20 women developed health problems of some kind, whilst Blomquist and Söderman[37] found that only 6 % of women had no problems (were asymptomatic) four months after delivery. Common health problems postpartum include UI and FI, depression, haemorrhoids, constipation, breast and perineal pain, dyspareunia, headaches, backache and exhaustion.[199] Physiotherapists are trained in pre- and postnatal care, and postgraduate courses are given all over the world. Thus, physiotherapists should be part of a multidisciplinary team in hospitals, maternity care centers and health care centers. The physiotherapist should promote health of the pregnant and postpartum women and on the motor development of the child. Additionally, this service should offer treatment of problems

that women experience in this period, to prevent these problems from being intolerable in later life.

CONCLUSIONS

Study I

There was no evidence that offering women a 12-week standard exercise program during the second half of pregnancy prevents GDM or improves insulin resistance in healthy pregnant women with normal BMI.

Study II

Women offered a 12-week exercise program during second half of pregnancy report LPP as frequently as women in the control group. However, regular exercise reduced the need for sick leave due to LPP. This supports the general advice that pregnant women should be encouraged to exercise during pregnancy.

Study III

Women offered a 12-week exercise program including PFMT reported less UI than control group women. The results document that pregnant women should be advised to do PFMT to prevent and treat UI. Thorough instruction in correct PFM contraction and PFMT is important, and specific PFM exercises should be included in exercise classes for pregnant women. The preventive effect of PFMT on AI should be further explored in future trials.

Study IV

The study showed that SenseWearTM Pro2 Armband provides a valid measure of energy expenditure during pregnancy. The instrument is feasible to use both in research and in a clinical setting.

IMPLICATIONS FOR FUTURE RESEARCH

Based on the present findings there is a need for further research during pregnancy:

- to study gestational endocrine changes and glucose homeostasis in general and insulin-stimulated glucose uptake in particular.
- to study exercise during pregnancy in women with high pre-pregnancy risk of developing GDM, such as increased BMI, previous GDM and a family history of T2DM.
- to study whether an early intervention including a consultation with a physiotherapist focusing on ergonomics and exercise instructions can prevent development of LPP and sick leave due to LPP.
- to study the efficacy of identify women at risk of LPP and to offer an individual follow-up.
- to study the etiology and pathophysiology of pregnancy related LPP.
- to study if PFMT in pregnancy can reduce AI in pregnancy.
- to study whether a dose-response or a threshold of physical activity and exercise training in pregnancy exists.

In this thesis, only short-term results are reported. Though, it is of importance to study the effects of regular exercise including PFMT during pregnancy on duration of labor, and long-term effects for both mother and child. In the TRIP trial there is ongoing postnatal assessments of growth and development of the children. In addition, the health of the mother is assessed. The follow-up is planned up to 20 years of age of the offspring and will give important information about the possible long-term effects of exercise during pregnancy.

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Paper I

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Paper II

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Paper III

Does regular exercise including pelvic floor muscle training prevent urinary and anal incontinence during pregnancy? A randomized controlled trial.

Running title: Exercise in pregnancy and prevention of incontinence

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ABSTRACT

Objective: To assess if pregnant women following a general exercise course including pelvic floor muscle training (PFMT) were less likely to report urinary and anal incontinence in late pregnancy than a group of women receiving standard care.

Design: A two-armed, two-center randomized controlled trial.

Setting: Trondheim University Hospital (St. Olavs Hospital) and Stavanger University Hospital in Norway.

Population: A total of 855 women were included in this trial.

Methods: The intervention was a 12-week exercise program, including PFMT, conducted between week 20 and 36 of pregnancy. One weekly group session was led by physiotherapists and home exercises were encouraged at least twice a week. Controls received regular antenatal care.

Main Outcome Measures: Self-reported urinary- and anal incontinence after the intervention period (at 32-36 weeks of pregnancy).

Results: Fewer women in the intervention group reported any weekly urinary incontinence (11% vs. 19%, p = 0.004). Fewer women in the intervention group reported fecal incontinence (3% vs 5%), but this difference was not statistically significant (p = 0.18).

Conclusions: The present trial indicates that pregnant women should exercise, and in particular do PFMT to prevent and treat urinary incontinence in late pregnancy. Thorough instruction is important and specific pelvic floor muscle exercises should be included in exercise classes for pregnant women. The preventive effect of PFMT on anal incontinence should be explored in future trials.

Keywords: Exercise, pregnancy, pelvic floor muscle training, incontinence, prevention, treatment.

Clinical trial registration: www.clinicaltrials.gov, NCT00476567.

INTRODUCTION

Pregnancy and delivery are risk factors for urinary and anal incontinence in later life.[1,2] Urinary incontinence is defined as "complaint of involuntary loss of urine",[3] while the term anal incontinence is defined as "complaint of involuntary loss of feces or flatus".[3]

The pelvic floor is an important part of the continence mechanisms.[4] Contraction of the pelvic floor muscles (PFM) causes an inward lift and squeeze around the urethra, vagina and rectum,[5] resulting in closure, stabilization, and resistance to downward movement.[6] Randomized controlled trials have documented the effects of intensive pelvic floor muscle training (PFMT) and close follow-up of physiotherapists in prevention and treatment of pregnancy related urinary incontinence.[7-11] Nevertheless, one Cochrane review and two other systematic reviews conclude that the effect of PFMT during pregnancy to prevent urinary and anal incontinence still is open to question.[12-14] The Cochrane review strongly recommends that all future trials of PFMT during pregnancy should collect data on fecal incontinence, and highlights the need for large, pragmatic trials of population-based approaches, using intensive PFMT and recruiting antenatal women regardless of continence status or parity.[12] There is a lack of trials investigating the effect of implementing PFMT in a more general training program for pregnant women.

We conducted the present study as one part of a randomized controlled trial aimed to investigate the effects of regular exercise during pregnancy in prevention of pregnancy-related diseases and complications during labour. The primary outcome was gestational diabetes and glucose metabolism.[15] Another important research question was whether it was possible to prevent urinary and anal incontinence by including specific PFM exercises in the general exercise course, to improve the continence mechanisms before the problem arise (primary prevention), and to detect incontinence at an early stage and thereby stop the development of the condition (secondary prevention).

The aim of this study was to assess if pregnant women following a general exercise course including PFMT, were less likely to report urinary and anal incontinence in late pregnancy than a group of women receiving standard care.

METHODS

We conducted a two-armed, two-center randomized controlled trial of a 12-week regular exercise program versus standard antenatal care. The procedures followed were in accordance with ethical standards of research and the Helsinki declaration. The women received written information about the trial, and they signed informed consent forms. The participants were not compensated financially. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 4.2007.81) and registered in Clinical trial gov (NCT 00476567).

Pregnant women booking for routine ultrasound at Trondheim University Hospital (St. Olavs Hospital) and Stavanger University Hospital were invited to participate in the trial. Women in Trondheim were recruited from April 2007 to June 2009, and women in Stavanger were recruited from October 2007 to January 2009. More than 97% of Norwegian pregnant women attend a routine scan at around 18 pregnancy weeks, and the exams are free of charge. During the inclusion period approximately 12 000 pregnant women had routine scans at the two hospitals. Inclusion criteria were age $\geq$ 18 years and a singleton live fetus. Exclusion criteria were high-risk pregnancies and/or diseases that could interfere with participation. For practical reasons we also excluded women who lived too far from the hospitals to attend weekly training groups (more than 30 minutes drive).

Concealed randomization in blocks of 30 was performed at the Unit for Applied Clinical Research, Norwegian University of Technology and Science, by a web-based computerized procedure. The staff involved with training or outcome assessments had no influence on the randomization procedure. Because of the nature of the study it was not blinded.

Women in the intervention group received a standardized exercise program including aerobic activity, strength training (including specific PFM exercises) and balance exercises. The training protocol followed recommendations from The American College of Obstetricians and Gynecologists and the Norwegian National Report on Physical Activity and Health.[16,17] Training sessions of 60 minutes in groups of 8-15 women instructed by a physiotherapist were offered once a week over a period of 12 weeks (between 20 and 36 pregnancy weeks). Each group session consisted of three parts:

1) 30-35 minutes low impact aerobics (no running or jumping). Step length and body rotations were reduced to a minimum, and crossing of legs and sharp and sudden changes of position were avoided. The aerobic dance program was performed at moderate intensity, defined as 13 and 14 on Borg's rating scale of perceived exertion.[18]

2) 20-25 minutes strength exercises using body weight as resistance, including exercises for the upper and lower limbs, back extensors, deep abdominal muscles and pelvic floor muscles. Three sets of ten repetitions of each exercise were performed.

3) 5-10 minutes of light stretching, body awareness, breathing and relaxation exercises.

In addition, women were encouraged to follow a written 45 minutes home exercise program including PFMT at least twice a week (30 minutes endurance training and 15 minutes strength and balance exercises).

Women in the intervention group were individually instructed in pelvic floor anatomy and how to contract the pelvic floor muscles correctly by a physical therapist. Correct contraction was controlled by vaginal palpation. The PFMT followed principles for increasing strength of skeletal muscles.[19] Women were encouraged to perform three sets of eight to twelve close to maximums contractions of the PFM and were encouraged to hold the contraction for six to eight seconds and if possible to add three fast contractions at the end of the contraction.[20] PFMT was performed in different positions with legs apart to emphasise specific strength training of the pelvic floor muscles and relaxation of other muscles.

Adherence to the protocol was defined as exercising three days per week or more on moderate to high intensity. Performing the exercise program was strongly emphasized and recorded in the women's personal training diary and through reports from the physiotherapists leading the training groups.

Women in the control group received standard antenatal care and the customary information given by their midwife or general practitioner. They were not discouraged from exercising on their own. Women in both groups received written information and recommendations on PFMT, diet and pregnancy related lumbopelvic pain. The PFMT brochure includes detailed information about the pelvic floor and an evidence-based PFMT program.[9]

Pre-tests were done between 18-22 weeks and post-tests between 32-36 weeks of pregnancy. Main outcomes were urinary and anal incontinence measured by self-reports. All participants answered a questionnaire including questions related to urinary (Sandvik's severity index)[21,22] and anal (St. Marks score)[23] incontinence at inclusion (18-22 weeks) and at the end of the intervention period (32-36 weeks). Women were asked to report their urinary leakage when A) coughing / sneezing / laughing, B) when being physically active (running or jumping), C) when sudden changes in position / lifting or D) leakage accompanied by a strong urgency to void. Answer alternatives were "Yes" or "No. Urinary leakage was subclassified according to the definitions given in the standardized terminology of lower urinary tract symptoms.[3] Women confirming any type of urinary leakage (alternative A, B, C or D) were referred to as having urinary incontinence (UI). Women confirming loss of urine in association with alternative A, B or C were defined as having stress urinary incontinence (SUI), while women confirming loss of urine with alternative D were defined as having urge urinary incontinence (UUI), The outcome measures of UI were further divided into two severity categories in respect to frequency, "urinary leakage < once per week" or "urinary leakage ≥ once per week (severe UI)". Anal incontinence was registered as fecal and flatal incontinence during the previous four weeks based on one question from the St. Marks score.[23] Women reporting leakage of solid and/or liquid stool during the last four weeks were categorized as fecal incontinent, and women reporting flatus during the last four weeks were categorized as flatal incontinent.

Frequency, intensity and type of physical activity including PFMT were recorded for both groups at inclusion and follow-up by self reports in a questionnaire. In addition, women in the intervention group registered PFMT in a training diary.

Based on a prevalence estimate of gestational diabetes of 9 % with a reduction to 4% (primary outcome of the trial), a study population of 381 patients in each group was needed in a two-sample comparison test with a 5% significance level and a power of 0.80. This sample size was able to detect a 0.2 SD difference on continuous variables with a power of 0.80. Given the study population, we had a power of 0.79 to detect a risk reduction in urinary incontinence of 10% from 50% to 40% in the two groups.

The statistical analyses were performed with SPSS version 19. The data were analyzed according to the "intention–to-treat" principle using Chi squared test and binary logistic regression. The results were presented as crude and baseline adjusted estimates with 95% confidence intervals.

Women in intervention and control groups were primarily analyzed according to type of incontinence (UI, SUI, UUI, fecal and flatal incontinence). Subgroup analyses were based on urinary, fecal and flatal continence status at the time of inclusion, estimating primary and secondary preventive effects of the intervention.

RESULTS

In all, 875 women consented to participate in the trial. Twenty women were excluded or withdrew before the first examination: thirteen did not meet the inclusion criteria, five miscarried and two had twin pregnancies. A total of 855 women were randomly allocated to an intervention group or a control group (Figure 1). However, 32 women in the intervention group and 61 in the control group were lost to follow-up. Data from 397 intervention group women and 365 control group women were included in a complete case analysis.

The groups were similar in baseline characteristics except for severe UI and SUI, which were more frequent in the control group (p = 0.05 and p = 0.01) (Table 1). After the intervention period significantly less women in the intervention group reported UI and SUI, irrespective of severity (Table 2). The findings were consistent when adjusting for baseline values. A lower proportion of women in the intervention group (3%) than the control group (5%) reported fecal incontinence, however the difference was not statistically significant (Table 2). There were no differences in weight or BMI between groups at follow-up.

Subgroup analyses were done for nulliparous and multiparous women. At baseline the prevalences of severe UI and SUI were lower in the intervention group among nulliparous women. After the intervention (at 32-36 weeks of pregnancy) the prevalence of UI was 35% vs. 47% with OR adjusted for baseline values 0.6 (95% CI 0.4, 0.9; p=0.03) in the intervention and control group among nulliparous women, and severe UI was 6% vs. 14%

with OR adjusted for baseline values 0.4 (95% CI 0.2, 0.9; p=0.02). In multiparous women the prevalence of fecal incontinence at 32-36 weeks of pregnancy was lower in the intervention group, 3% vs. 8% with OR adjusted for baseline values 0.2 (95% CI 0.1, 0.8; p=0.03). No other significant differences were seen in a subgroup analysis according to parity.

Baseline characteristics of subgroups based on groups stratified according to urinary continence status at inclusion are presented in Table 3. Sixty-nine percent of the continent women and 40% of the incontinent women were nulliparous. The subgroup analyses showed that in women who were continent for urine at inclusion, the proportions of women reporting SUI $\geq$ once per week and UUI were significantly lower (p = 0.03 and p = 0.006) in the intervention group after the intervention period (Table 4). Furthermore, in women in either group who were incontinent for urine at inclusion, the proportion reporting UI, UI $\geq$ once per week and SUI after the intervention period was lowest in the intervention group (p = 0.002, p = 0.03 and p = 0.007). The findings were consistent when adjusting for baseline values (Table 4).

There were no differences in age, parity, weight and BMI based on groups stratified according to fecal continence status at inclusion. Among fecal continent women at inclusion, 2% (8/359) in the intervention group and 4% (13/332) in the control group reported fecal incontinence at follow-up with an OR and 95% CI of 0.6 (0.2, 1.4; p = 0.20). Among women reporting fecal incontinence at inclusion, 19% (4/21) in the intervention group and 20% (3/15) in the control group reported fecal incontinence at follow-up with and OR and 95% CI of 0.9 (0.2, 5.0; p = 0.94).

Women reporting flatal incontinence at inclusion were younger than flatal continent women (30.0 ± 4.1 versus 30.7 ± 4.4) and a larger proportion was nulliparous (65% versus 54%). Among flatal continent women at inclusion the proportion flatal incontinence in both groups after the intervention period were 21% (58/275 versus 53/258) with an OR and 95% CI of 1.0 (0.7, 1.6; p = 0.88). Among women reporting flatal incontinence at inclusion, 69% (75/109) in the intervention group and 74% (69/93) in the control group reported flatal incontinence at follow-up with and OR and 95% CI of 0.8 (0.4, 1.4; p = 0.40).

In the intervention group, 95% reported weekly PFMT at follow-up compared to 79% in the control group (p < 0.001). The proportion of intervention group women performing PFMT three times per week or more was 67% compared to 40% in the control group (p < 0.01).

Adherence to the general exercise protocol (exercising three days per week or more at moderate to high intensity) in the intervention group was 55% (n = 217). For comparison 10% in the control group exercised three days per week or more at moderate to high intensity at follow-up (p < 0.001). In the intervention group, 72% exercised at least once per week. UI and anal incontinence were not more frequent among the protocol adherent intervention group women (n = 217) compared to the total control group at the end of the intervention.

No serious adverse events related to physical exercise were seen, and the outcomes of pregnancy were similar in the two groups.[15]

DISCUSSION

This trial demonstrates that pregnant women following a 12-week regular exercise course including PFMT were less likely to report UI and SUI in late pregnancy than women given standard care including written instructions in PFMT. Among pregnant women being continent for urine at the time of inclusion, significantly fewer women in the intervention group reported SUI once per week or more and UUI at follow-up, indicating a primary preventive effect of the intervention. In the subgroup of pregnant women categorised as incontinent for urine at inclusion, significantly fewer women in the intervention group reported UI, SUI once per week or more and SUI in late pregnancy compared to women in the control group (secondary prevention). A lower proportion of women in the intervention group reported fecal incontinence compared to the control group, however the difference was not statistically significant. A subgroup analysis of multiparous women showed a significantly lower prevalence of fecal incontinence in the intervention group after the intervention.

Strengths of the present trial are the large number of participants, the high follow-up rate and the use of a computerized randomization procedure. Despite the randomized design some of the baseline characteristics were significantly different between groups. This was probably

due to chance and accounted for in the statistical analysis. The investigators were aware of group allocation. However, since prevalence of incontinence was based on self-reports the lack of blinding of investigators should not have had any impact on the results. The prevalence of urinary leakage in pregnancy has been reported to vary between 9% and 74%.[24,25] This variation is probably due to different study populations (various proportions of nulliparous/parous women), different definitions of incontinence (self-reports or standardised pad tests), and different pregnancy lengths. In the Norwegian Mother and Child Cohort Study including 43,279 women from 1999-2006, 58% of the women reported any UI and 35% any UI weekly or more in pregnancy week 30.[26] Anal incontinence is less studied in pregnancy, but a prevalence of 6% in late pregnancy has been reported.[27]

The prevalence of urinary leakage in mid- and late pregnancy in the present trial was lower than in a previous trial conducted in the same geographically area ten years ago using the same outcome measures to classify continent and incontinent women as in the present trial.[9] Mørkved et al found that 32% of nulliparous women in the intervention group and 48% in the control group reported leaking urine once per week or more in pregnancy week 36.[9] In the present trial leaking urine once per week or more in pregnancy week 32-36 was reported by 6% vs. 14% nulliparous women. Since PFMT is known to have a high cure rate,[28] the difference between studies may be due to an increased focus on PFMT in pregnant women and health care professionals, following the results of the previous trial. In the current trial 60% of the study participants reported doing any PFMT at the time of inclusion, and 25% reported doing PFMT three times per week or more. In the previous trial 30% performed any PFMT at inclusion.[9]

The success of training depends on the ability to effectively contract the PFM. It is estimated that 30 % of women are unable to contract the PFM on the first attempt.[29,30] Bump et al[29] found that only 49 % performed an ideal voluntary PFM contraction after brief standardized verbal instruction. In the present trial all women in the intervention group were individually instructed in pelvic floor anatomy and correct contraction was controlled with vaginal palpation. Women in both groups received written information of PFMT including an evidence-based exercise program, and at follow-up, the number of women performing PFMT had increased in both groups. At follow-up, a large proportion of women in the control group reported doing regular PFMT during the intervention period. Still, the intervention group

demonstrated significantly less UI in late pregnancy. This finding suggests that thorough instructions in correct PFM contraction, intensive PFMT and close follow-up are important to increase the success rate.

Another possible explanation of a low prevalence in the current trial may be differences in study populations. In the trial by Mørkved et al[9] pregnant women were invited to participate with the explicit goal to study the effects of PFMT on urinary incontinence. The aims of the current trial were to assess effects of a more general exercise program on several pregnancy-related conditions. Women experiencing urinary leakage may have been more likely to sign up in the previous trial aiming to improve continence, and women with severe urinary leakage may have been less likely to sign up for a general exercise trial including activities or situations that often cause incontinence. In the previous trial 32 % of the study population reported weekly UI at inclusion[9] compared to 13 % in the current trial. The study population in the present trial was found to be representative for pregnant women in Norway regarding age, BMI, parity and level of exercise.[15]

Three previous trials have addressed primary prevention of UI during pregnancy.[8,31,32] Two trials reported highly significant preventive effects of PFMT.[8,32] The third trial had conflicting results,[31] but the response rate of participants was low (ca 50%). The Cochrane review addressing prevention of urinary- and fecal incontinence included mixed prevention and treatment trials.[12] Data from subgroups of previously continent women[7,9] were added to the analyses of a primary preventive effect of PFMT on UI, and the results documented that for women having their first baby, antenatal PFMT appears to reduce the prevalence of urinary incontinence in late pregnancy.[12] Thus, the review suggested new large, pragmatic trials using intensive PFMT and recruiting antenatal women regardless of continence status or parity and collecting data on both urinary and fecal incontinence.[12] Subgroup analyses in the present trial support the Cochrane review conclusions that the prevention and treatment effects on UI in late pregnancy were predominantly seen in women having their first baby with a 40-60% reduction in risk.

Anal incontinence is less prevalent, but this condition is clearly a social and psychological burden, which reduces the quality of life.[33] The preventive effect of PFMT on the

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development of anal incontinence is sparsely studied. One previous trial included PFMT in a general fitness program. This trial demonstrated no difference in urinary- or anal incontinence between intervention and control group. However, this trial was underpowered and included no control of the women's ability to contract the PFM correctly.[34]

In the present trial, the proportion of women reporting fecal incontinence in the intervention group was reduced from 5% to 3% after the intervention period. In the control group the proportion reporting fecal incontinence increased from 4% to 5% at follow up. Although this difference was not statistically significant, it may suggest a possible clinically significant effect of the intervention. Another interesting finding was the preventive effect on fecal incontinence in multiparous women. This finding indicates that in women with possible previous birth related injury to the PFM, PFMT might prevent fecal incontinence in a later pregnancy.

In the present trial, women in the intervention group were encouraged to follow a general exercise protocol three times per week or more during the 12-week intervention period. Fiftyfive percent of the women in the intervention group adhered to the protocol and 72% of intervention group women exercised at least once per week. For comparison, 10% of control group women reported exercising three days per week or more and 30% at least once per week. Women being physically active are more frequently exposed to higher and more repetitive increases in abdominal pressure compared to more sedentary women. The exercise protocol in the present trial was physical fitness exercises designed for pregnant women and did not include running or jumping. However, the aerobic part of the program consisted of weight bearing exercises causing increased abdominal pressure and increased risk of urinary leakage. Nevertheless, fewer women in the intervention group reported UI, and women adhering to the exercise protocol reported less UI than non-adherent women in the intervention group at follow-up.

In addition to better structural support for the bladder neck with PFMT, the intervention group may have developed increased awareness and skill of timing the contraction with the event that elicits leakage. Miller et al[35] found that 80% of women with de novo stress incontinence in pregnancy week 35 were able to reduce leakage during coughing by using the Knack

maneuver (i.e. tighten the PFM in preparation for a known leakage-provoking event), with 55% eliminating leakage completely.

An epidemiologic study including 27,936 women reported a prevalence of any urinary incontinence of 25% in the adult population, with the prevalence of incontinence increasing with age.[36] Among nulliparous women in that study (n = 3,339) 10% reported UI.[37] Data suggest that pregnancy contributes to pelvic floor dysfunction later in life,[38] and that the first pregnancy and delivery is associated with a high prevalence of objective and subjective bowel dysfunction.[39] In a cohort study it was found that most women experiencing postpartum UI had symptoms of UI during the third trimester.[25] Another study found that five years after the first delivery, 33% of women reported UI.[40] Although UI is common, it reduces quality of life and affects social, physical, occupational and leisure activities.[41] The present trial demonstrates that PFMT during second half of pregnancy reduced the prevalence of UI in late pregnancy. However, it is important to assess any possible long-term effects postpartum. When comparing the prevalence of UI in the present trial with one previous trial from the same area,[9] we found a significant reduction over the last ten years. This may be due to different study populations, but may also be due to increased awareness and knowledge about prevention and treatment of UI among health care professionals and the general population, indicating a preventive effect of information, instructions and encouragement to exercise the PFM.

The prevalence of fecal incontinence during pregnancy is low, and the present trial was slightly underpowered to assess fecal incontinence properly, as shown by the wide confidence intervals. One important issue for future research is to assess if PFMT in pregnancy can reduce fecal incontinence in pregnancy. Further, it is important to assess the effects of regular exercise including PFMT during pregnancy on duration of labour, the long-term effects on urinary- and anal continence and to investigate the associations between outcome, prior continence status and parity.

CONCLUSION

The results from the present trial indicate that pregnant women should do PFMT to prevent and treat UI in late pregnancy. Thorough instruction in correct PFM contraction and PFMT is important, and specific PFM exercises should be included in exercise classes for pregnant women. Any possible long-term effects on UI and the preventive effect of PFMT on anal incontinence should be further explored.

Disclosure of Interests

None of the authors have a conflict of interest.

Contribution to authorship

- Signe N. Stafne, physiotherapist, PhD-student. Participated in planning of the main study, coordinated the data collection, organized the training program, analyzed the data, wrote the first draft and finalized the manuscript.
- Kjell Å. Salvesen, Professor of obstetrics and gynaecology, PhD. Participated in the planning of the main study, revising and finalizing the manuscript.
- Pål R. Romundstad, Professor of epidemiology, PhD. Participated in the data analyses, revising and finalizing the manuscript.
- Irene Hiim Torjusen, physiotherapist. Participated in the interpretation of data, revising and finalizing the manuscript.
- Siv Mørkved, Professor of physiotherapy, PhD. Principal investigator, initiated and planned the main study, supervised the training program, participated in the interpretation of the data as well as drafting and finalizing the manuscript.

Details of Ethics Approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 4.2007.81).

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Table 1. Baseline maternal characteristics of the study population.

Maternal characteristics	Intervention group (n = 429)	Control group (n = 426)
Mean age – years	30.5 ± 4.4	30.4 ± 4.3
Parity – no. (%)		
0	247 (58)	239 (56)
1	125 (29)	129 (30)
2+	57 (13)	58 (14)
Previous vaginal delivery – no. (%)	168 (39)	171 (40)
Gestational week at booking	20.3 ± 1.5	20.3 ± 1.7
Booking BMI – kg/m^2	24.7 ± 3.0	25.0 ± 3.4
Booking weight – kg	70.4 ± 9.8	70.8 ± 10.3
Exercise regularly – no. (%)	228 (53)	216 (51)
Exercise regularly ≥3 times per week at moderate to high intensity – no. (%)	60 (14)	50 (12)
PFMT – no. (%)	249 (59)	272 (64)
PFMT ≥3 times per week – no. (%)	101 (24)	110 (26)
UI *	172 (40)	180 (43)
UI ≥1 times per week – no. (%) *	44 (10)	63 (15)
SUI †	108 (26)	120 (30)
SUI ≥1 times per week – no. (%) †	23 (5)	43 (10)
UUI	16 (4)	16 (4)
UUI ≥1 times per week – no. (%)	1 (0.2)	2 (0.5)
Fecal incontinence – no. (%) ‡	22 (5)	17 (4)
Flatal incontinence – no. (%) §	118 (28)	111 (27)

Plus-minus values are means ± SD.

BMI denotes Body Mass Index, PFMT pelvic floor muscle training, UI any urinary incontinence, SUI stress urinary incontinence and UUI urge urinary incontinence.

* Data missing in 0.5% of cases.

† Data missing in 3.6% of cases.

‡ Data missing in 2.5% of cases.

§ Data missing in 2.0% of cases.

Table 2. Urinary incontinence (UI) at 32-36 weeks of pregnancy in the intervention group and control group including both women with and without urinary leakage at inclusion.

	Intervention group N = 397		Control group N = 365		Unadjusted			Adjusted for baseline values		
	n	%	n	%	OR	95% CI	p-value	OR adjusted	95% CI	p-value
UI *	166	42	192	53	0.7	(0.5, 0.9)	0.004	0.6	(0.4, 0.9)	0.004
UI ≥1 time per week *	44	11	68	19	0.5	(0.4, 0.8)	0.004	0.5	(0.3, 0.8)	0.006
SUI †	102	28	128	37	0.7	(0.5, 0.9)	0.01	0.7	(0.5, 0.9)	0.02
SUI ≥1 time per week †	25	7	45	13	0.5	(0.3, 0.8)	0.006	0.5	(0.3, 0.9)	0.03
UUI ‡	11	3	20	6	0.5	(0.2, 1)	0.06	0.4	(0.2, 0.9)	0.04
UUI ≥1 time per week ‡	0	0	3	1	1	(1, 1)	0.07	-	-	-
Fecal incontinence §	12	3	18	5	0.6	(0.3, 1.3)	0.18	0.6	(0.3, 1.4)	0.24
Flatal incontinence l	136	35	124	35	1	(0.7, 1.4)	0.97	0.9	(0.7, 1.3)	0.73

UI denotes any urinary incontinence, SUI stress urinary incontinence and UUI urge urinary incontinence.

* Data missing in 0.7% of cases

† Data missing in 6.0% of cases

‡ Data missing in 1.0% of cases

§ Data missing in 2.8% of cases

l Data missing in 2.2% of cases

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Table 3. Baseline characteristics of subgroups stratified according to continence status at inclusion.

	Intervention group		Control group	
	Continent	Incontinent	Continent	Incontinent
	N = 256	N = 172	N = 244	N = 180
Mean age – years	30.1 ± 4.0	31.2 ± 4.9	30.0 ± 4.4	31.0 ± 4.1
Parity – no. (%)				
0	177 (69)	69 (40)	166 (68)	72 (40)
1	50 (20)	75 (44)	56 (23)	72 (40)
2+	29 (11)	28 (16)	22 (9)	36 (20)
Booking weight – kg	70.0 ± 10.0	71.0 ± 9.5	70.3 ± 10.1	71.6 ± 10.7
Booking BMI – kg/m^2	24.5 ± 3.0	24.9 ± 3.1	24.9 ± 3.4	25.2 ± 3.5
UI	-	172 (100)	-	180 (100)
UI ≥1 times per week – no. (%)	-	44 (26)	-	63 (35)
SUI	-	108 (67)	-	120 (74)
SUI ≥1 times per week – no. (%)	-	23 (14)	-	43 (26)
UUI	-	16 (9)	-	16 (9)
UUI ≥1 times per week – no. (%)	-	1 (0.6)	-	2 (1)

Plus-minus values are means ± SD.

BMI denotes Body Mass Index, UI any urinary incontinence, SUI stress urinary incontinence and UUI urge urinary incontinence.

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Table 4. Subgroup analysis of urinary incontinence (UI) at 32-36 week of pregnancy in the intervention group and control group. Subgroups are based on groups stratified according to continence status at inclusion.

	Intervention group		Control group		OR	95 % CI	p-value	Adjusted for baseline		
	n	%	n	%				OR	95 % CI	p-value
Continent at inclusion	*N = 235*		*N = 208*							
UI	55	23	59	28	0.8	(0.5, 1.2)	0.23			
UI ≥ 1 time per week	6	3	13	6	0.4	(0.1, 1)	0.06			
SUI	38	17	40	20	0.8	(0.5, 1.4)	0.49			
SUI ≥ 1 time per week	3	1	10	5	0.3	(0.1, 1)	0.03			
UUI	2	1	11	5	0.2	(0.03, 0.7)	0.006			
UUI ≥ 1 time per week	0	0	1	0.5	1	(1, 1)	0.29			
Incontinent at inclusion	*N = 157*		*N = 156*							
UI	111	71	133	85	0.4	(0.2, 0.7)	0.002	0.4	(0.2, 0.7)	0.002
UI ≥ 1 time per week	38	24	55	35	0.6	(0.4, 1)	0.03	0.5	(0.3, 1)	0.04
SUI	64	45	88	61	0.5	(0.3, 0.8)	0.007	0.5	(0.3, 0.8)	0.008
SUI ≥ 1 time per	22	15	35	24	0.6	(0.3, 1)	0.06	0.7	(0.3, 1.3)	0.20

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	week									
UUI	9	6	9	6	1	(0.4, 2.5)	0.97	0.8	(0.3, 2.5)	0.77
UUI ≥ 1 time per week	0	0	2	1	1	(1, 1)	0.15	-	-	-

UI denotes any urinary incontinence, SUI stress urinary incontinence and UUI urge urinary incontinence.

Figure legend

Figure 1. Flow chart of study participants.

Word count:

Abstract: 249

Manuscript: 3979

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┌─────────────────────┐                ┌──────────────────────────────────┐
│   Enrollment        │                │  Assessed for eligibility (n=875)│
└─────────────────────┘                └──────────────────────────────────┘
                                                         │
                                                         │      ┌──────────────────────────────────┐
                                                         ├─────▶│  Excluded (n=20)                 │
                                                         │      │  ☐  Twin pregnancies (n=2)       │
                                                         │      │  ☐  Miscarried (n=5)             │
                                                         │      └──────────────────────────────────┘
                                                         ▼
                                              ┌──────────────────────┐
                                              │  Randomized (n=855)  │
                                              └──────────────────────┘
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                        ┌──────────────┐
                        │  Allocation  │
                        └──────────────┘
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| Allocated to intervention group (n=429) | Allocated to control group (n=426) |

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                        ┌──────────────┐
                        │  Follow-Up   │
                        └──────────────┘
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Lost to follow-up during pregnancy (n=33)

♦ Gave birth before scheduled T2 (n=4)

♦ Medical reasons (n=1)

♦ Illness (n=4)

Lost to follow-up during pregnancy (n=61)

♦ Gave birth before scheduled T2 (n=7)

♦ Medical reasons (n=1)

♦ Illness (n=2)

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                        ┌──────────────┐
                        │  Analysis    │
                        └──────────────┘
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| Assessed in pregnancy week 32-36 (n=396) | Assessed in pregnancy week 32-36 (n=365) |

Paper IV

APPENDICES I-IV

Appendix I

SJEKKLISTE FOR INKLUSJON
- *"Effekt av trening under svangerskap"*

	Spørsmål	JA	NEI
1.	Kvinne >18 år?	●	
2.	Bopæl nær sykehuset (<20 km)	●	
3.	Kaukasisk, snakker norsk	●	
4.	Normal graviditet med lav risiko for svangerskapskomplikasjoner	●	
5.	Informert skriftlig samtykke	●	
6.	Diabetes?		●
7.	Tidligere alvorlig svangerskapskomplikasjoner *-preterm fødsel før uke 34* *-tidlig innsettende og alvorlig preeklampsi (dvs forløsning før uke 34 eller eklampsi og HELLP syndrom)* *-alvorlig vekstretardasjon hos foster*		●
8.	Alvorlig kroniske sykdommer *-astma* *-hjertesykdom* *-SLE* *-hypertoni (medikamentelt behandlet før graviditet)* *-alvorlig nyresykdom*		●
9.	Kjent alkohol- eller medikamentmisbruk		●
10.	Flerlinger		●
11.	Fostermisdannelser		●
12.	Placenta previa		●
13.	Forhøyet blodtrykk (>140/90) i minst to målinger før sv.uke 20		●
14.	Identifisert høy risiko for preterm fødsel *-kort livmorhals* *-rikelige vaginalblødninger med påvist retroplacentært hematom* *-vannavgang eller fostervannslekkasje*		●
15.	Uegnet til å delta av enhver annen årsak		●

BORGS SKALA

INSTRUKSJON

I løpet av treningen vil vi at du skal være oppmerksom i forhold til hvor anstrengende du føler at treningen er. Denne følelsen skal gjenspeile totalsummen av anstrengelse og utmattelse, ved å kombinere alle følelser av fysisk stress, påkjenning og utmattelse. Ikke bry deg om hver enkelt faktor slik som smerte i beina, kortpusthet eller øvelsens intensitet, men forsøk å konsentrere deg om den totale indre følelsen av anstrengelse. Prøv å ikke undervurdere eller overvurdere din følelse av anstrengelse; men vær så presis som du kan.

BORGS SKALA

6

7 Meget, meget lett

8

9 Meget lett

10

11 Ganske lett

12

13 Litt anstrengende

14

15 Anstrengende

16

17 Meget anstrengende

18

19 Svært anstrengende

20

Appendix III

PROGRAM FOR EGENTRENING

Egentreningsprogrammet består av to deler, både utholdenhetstrening (30 min) og styrketrening (ca 15 min).

Utholdenhetstreningen kan oppnås på ulike måter, men det er viktig at du finner en treningsform som passer deg. Du kan gå rask tur, jogge, sykle, svømme eller annet. Det viktigste er at du får økt puls over lengre tid (30 min). Intensiteten skal være såpass at det oppleves *litt anstrengende*, det vil si at du skal bli varm og svett.

Styrketreningsprogrammet består av sju ulike øvelser som har til hensikt å styrke ben, armer, rygg, mage, bekkenbunnsmuskulatur samt trene balansen. På alle øvelsene er det beskrevet flere mulige utgangsstillinger for gjennomføring. Det er viktig at du prøver deg litt fram og finner den utgangsstillingen som passer best for deg. Spør gjerne fysioterapeuten som leder gruppetreningen om hjelp til dette. Det vil være naturlig at en utgangsstilling som passer deg bra i begynnelsen av treningsperioden, passer mindre bra mot slutten av treningsperioden enten fordi magen har blitt større, du har blitt sterkere eller noe oppleves ubehagelig. Da kan du bytte til en annen utgangsstilling.

Det er viktig at du klarer å gjennomføre hver øvelse med *8-12 repetisjoner og 3 serier*.

Underveis eller etter treningen skal du ikke ha noe ubehag. Det er naturlig å være litt støl i etterkant av treningen, spesielt i oppstartsfasen, men du skal ikke ha smerter. Ta kontakt dersom noe medfører ubehag.

Hjemmetreningsprogrammet skal gjøres *to dager i uka* i tillegg til en time i gruppetrening med fysioterapeut.

OBS! Husk å krysse av på treningsdagboken når du har gjennomført treningen.

Øvelse 1

KNEBØY

Alt. A)
Stå med skulderbreddes avstand med føttene. La armene henge ned eller plasser de på hoftekammen. Bøy ned i hofte- og kneledd med "knær over tær", og rumpa ut bak som om du skal sette deg på en stol. Stram setet og strekk opp igjen til stående stilling. Varier tyngden med hvor langt du bøyer ned.

Øvelsen kan også gjøres stående på balanseputa.

Alt. B)
Strekk armene fram mens du bøyer ned.

Øvelsen kan også gjøres stående på balanseputa.

Øvelse 2

"PLANKEN" (gjøres tre ganger)

Alt. a)
Grunnstilling
Stå på alle fire (knær og strake armer) med ryggen i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen) og hold posisjonen i 10-15 sek.
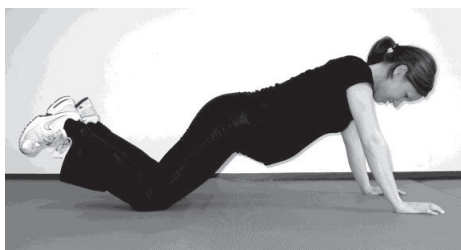
Alt. b)
Start med grunnstillingen. Trekk navlen inn mot ryggen (nedre del av magen) og finn stillingen som bildet viser: Stå på knær og strake armer, hold kroppen strak og ryggen i nøytral stilling. Hold posisjonen i 10-15 sek.
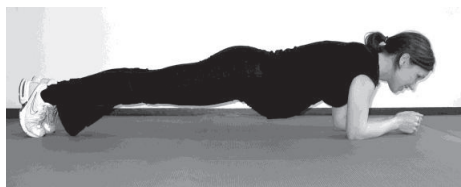
Alt. c)
Start med grunnstillingen. Trekk navlen inn mot ryggen (nedre del av magen) og finn stillingen som bildet viser: Stå på tærne og albuene, hold kroppen strak og ryggen i nøytral stilling. Hold posisjonen i 10-15 sek.

OBS!
Pust godt mens du gjør øvelsen (ikke hold pusten)!

Dersom du ikke klarer å holde posisjonen må du gå bytte til en enklere utgangsstilling eller korte ned holdetiden!

Dersom du har god kontroll på øvelsen kan du gjøre den tyngre ved å stå på balanseputa. Ha puta under knærne i utgangsstilling a og b, eller under tærne i utgangsstilling c.

Øvelse 3

<u>ARMHEVINGER</u>

Alt. a)
Stå med føttene i skulderbreddes avstand et stykke ut fra veggen. Len deg mot veggen på strake armer med strak kropp. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen"). Gjør armhevinger mot veggen. Varier tyngden med å stå nærmere veggen (lettere) eller lenger fra veggen (tyngre).
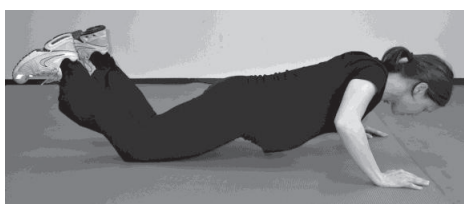
Alt. b)
Stå på knær og strake armer. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen").
Gjør armhevinger med knærne i gulvet og strak kropp.

Alt. c)
Stå på tær og strake armer. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen"). Gjør armhevinger med tærne i gulvet og strak kropp.

Øvelse 4

<u>DIAGONALLØFT</u>

Alt. a)
Stå på knær og strake armer med hodet i nøytral stilling. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen"). Løft diagonalt arm og ben til vannrett stilling.

<u>Alternativ ved smerter:</u>
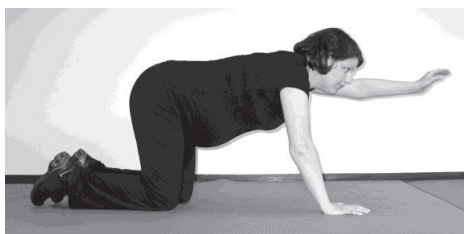
Alt. b)
Stå på knær og strake armer med hodet i nøytral stilling. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen"). Løft en og en arm strakt frem.

Alt. c)
Stå på knær og strake armer eller på albuene med hodet i nøytral stilling. Trekk navlen inn mot ryggen (<u>nedre del av magen</u>, se "Plankeøvelsen"). Strekk et og et ben vannrett bakover.

Øvelse 5

<u>BEKKENBUNNENS MUSKLER</u>

Løft opp og inn rundt urinrør, skjede og endetarm uten å spenne mage, sete og lår. Ta i så hardt du kan under hver sammentrekning og forsøk å holde i 6-8 sekunder før du slipper rolig ned. Pust rolig ut og inn, både under og mellom muskelsammentrekningene. Velg en eller flere av disse utgangsstilingene:

Alt. a)
Sitt med bena fra hverandre i skredderstilling med rett rygg. Trekk sammen rundt åpningene i bekkenbunnen.

Alt. b)
Stå med bena fra hverandre, kjenn etter at du er slapp i setemusklene mens du trekker sammen i bekkenbunnsmusklene.

Alt. c)
Stå på alle fire med knærne ut til siden og føttene sammen. Hev bekkenbunnen opp og innover.

Øvelse 6

SKRÅ BUKMUSKLER

Alt. a)
Skrå sit-ups i sittende. Sitt i skredderstilling med rett rygg. Press motsatt arm og kne mot hverandre. Bruk strak arm og press diagonalt.
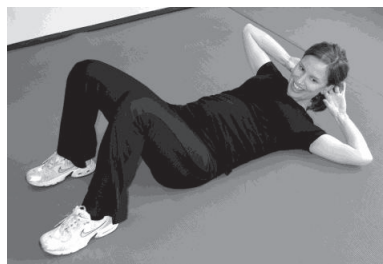
Alt. b)
Skrå sit-ups i ryggliggende. Ligg på ryggen med bøyde ben og korsryggen i kontakt med gulvet. Løft overkroppen litt opp fra underlaget slik at skulder peker mot motsatt kne.

OBS!
Noen gravide kan bli uvel eller svimmel av å ligge på ryggen. Dersom det gjelder deg bør du trene de skrå bukmusklene i utgangsstilling a.

Trekk sammen bekkenbunnsmusklene samtidig som du gjør skrå sit-ups.

Øvelse 7

<u>BALANSEØVELSER</u>

Alt. a)
Stå med begge ben på balanseputa. Stabiliser mage og rygg ved
å trekke navlen inn mot ryggen (<u>nedre del av magen</u>, se
"Plankeøvelsen").
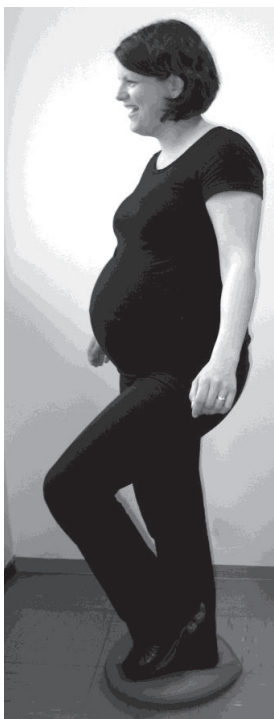
Alt. b)
Stå med ett ben på balanseputa. Stabiliser mage og rygg ved å
trekke navlen inn mot ryggen (<u>nedre del av magen</u>, se
"Plankeøvelsen").

Alt. c)

Stå på balanseputa i valgfri utgangsstilling. Stabiliser mage og rygg ved å trekke navlen inn mot ryggen (nedre del av magen, se "Plankeøvelsen"). Hold balansen mens du:

✓ Lukker øynene
✓ Strekker deg i ulike retninger
✓ Kaster en ball mot en vegg og tar imot
✓ Har en gjenstand i hånden og bytt over til andre hånden foran, over og bak kroppen
✓ Gjør knebøy (øvelse 1) med lukkede øyne

Forespørsel om å delta i en vitenskapelig undersøkelse

EFFEKT AV TRENING I SVANGERSKAPET I FOREBYGGING OG BEHANDLING AV SVANGERSKAPSRELATERT SYKDOM

Studien er et samarbeidsprosjekt mellom Kvinneklinikken ved St.Olavs Hospital og NTNU

ID-nummer:

(fylles ut av prosjektkoordinator)

Hvis du ønsker å delta, må du fylle ut dette samtykkeformularet. Samtykkeformularet leveres til prosjektkoordinator ved oppmøte for første test.

SAMTYKKEERKLÆRING FOR PROSJEKTET "EFFEKT AV TRENING I SVANGERSKAPET"

Jeg har lest informasjonsskrivet, og har hatt anledning til å stille spørsmål. Jeg er også informert om at journalopplysninger fra det aktuelle svangerskap og fødsel vil bli gjennomgått og registrert, og samtykker i å delta i studien.

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Sted og dato ………………………………

_____
Underskrift

Bakgrunn og målsetting

I løpet av 2007 og 2008 gjennomføres et forskningsprosjekt ved St. Olavs Hospital, med målsettingen å øke kunnskapen om helsen hos gravide. Undersøkelsen tar sikte på å finne ut mer om effekter av trening under svangerskapet, i forebygging og behandling av svangerskapsrelatert sykdom (svangerskapsdiabetes, overvekt, høyt blodtrykk, rygg- og/eller bekkenrelaterte smerter, urin- og/eller avføringslekkasje). Dessuten vil vi undersøke om treningen påvirker fødselen.

Hvem kan delta, og hva innebærer deltakelse

Alle friske gravide kvinner (18 år eller mer), som innkalles til rutinemessig ultralydundersøkelse i 18. svangerskapsuke, og har bopel innen 20 km fra sykehuset, inviteres til å delta i studien. For at vi skal få vite mer om helsetilstanden generelt, og om helsen i svangerskapet spesielt, ber vi om å ta blodprøver av alle deltakerne i prosjektet, og at alle svarer på spørreskjema og gjennomfører enkelte tester. Testingen foregår på svangerskapspoliklinikken ved St. Olavs Hospital i svangerskapsuke 20 og 32, samt tre måneder etter fødselen. Du må være på sykehuset i ca tre timer fordi det skal gjøres en sukkerbelastningstest, der blodprøvene skal tas med to timers mellomrom. I mellomtiden fyller du ut et spørreskjema, og en fysioterapeut utfører tester på deg av ryggen, bekkenet, balansen og styrken på bekkenbunnens muskulatur. Du møter fastende til testingen og vil bli tilbudt mat etterpå. Dessuten ber vi om at vi får benytte informasjon om vekt og blodtrykk fra svangerskapsjournalen, og opplysninger om fødselsforløpet og barnets vekt og lengde fra fødselsjournalen. Enkelte tilfeldig utvalgte av deltakerne vil bli spurt om å delta i en kondisjonstesting og i en ultralydundersøkelse av bekkenbunnsmusklene og magemusklene.

Når det gjelder trening under svangerskapet, vet man ennå ikke sikkert om svangerskapsproblemer kan behandles og forebygges, og eventuelt hvilke tiltak som har best effekt. Deltakerne i denne undersøkelsen blir derfor tilfeldig fordelt i to grupper. En datamaskin avgjør ved loddtrekning (randomisering) hvilken behandling du skal ha. Du får et tilfeldig nummer i databasen, og bare prosjektkoordinator kjenner koblingen mellom nummeret i databasen og din identitet. Deltakerne i den ene gruppen får den informasjonen som nå gis rutinemessig til gravide. Den andre gruppen er en treningsgruppe, hvor deltakerne skal delta i en times fellestrening ledet av fysioterapeut en gang i uken, og gjennomføre et enkelt program for egentrening på 45 minutter to ganger i uken. Treningen gjennomføres mellom uke 20 og 36 i svangerskapet.

Etter at forskningsprosjektet er avsluttet, vil alle deltakere få skriftlig informasjon om resultatene. Hvis trening viser seg å ha god effekt som behandling og forebygging, vil deltakerne i kontrollgruppen få informasjon om treningsprogrammet etter at prosjektet er avsluttet. For å kunne undersøke langtidsvirkningen av trening/ikke-trening under svangerskapet, ber vi om samtykke til at data oppbevares i 20 år, slik at vi kan kontakte deltakerne igjen for eventuelle oppfølgingsstudier vedrørende egen og barnets helse i årene etter fødselen.

Frivillighet og samtykke

• Deltakelse i prosjektet er frivillig.
• Alle deltakere i prosjektet har rett til å trekke seg fra prosjektet når de måtte ønske, uten at dette får konsekvenser for videre oppfølging og behandling.
• All informasjon deltakerne gir i forbindelse med prosjektet, behandles konfidensielt, og data avidentifiseres. Alle som skal ha kontakt med de innsamlede data, er underlagt taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21.
• Deltakerne er dekket av Pasientskadeerstatningsordningen.

Etisk og faglig vurdering

• Prosjektet er vurdert av Regional komite for medisinsk forskningsetikk, Region Midt-Norge, og komiteen har godkjent at prosjektet gjennomføres.
• Prosjektet er meldt til personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste.

Ansvarlige prosjektledere er seksjonsoverlege ved Fødeavdelingen, St. Olavs Hospital, Kjell Åsmund Salvesen, forskningsrådgiver ved Klinikk for kliniske servicefunksjoner, St. Olavs hospital, Siv Mørkved og doktorgradsstipendiat ved Institutt for samfunnsmedisin, NTNU, Signe Nilssen Stafne.

HVIS DU ØNSKER Å DELTA, ELLER HAR SPØRSMÅL OM PROSJEKTET, BES DU KONTAKTE:

Signe Nilssen Stafne (prosjektkoordinator)

Du kan ta kontakt på følgende måte:
• E-post: signe.n.stafne@ntnu.no
• Send SMS til 46 85 62 67. Skriv prosjekt, ditt navn og telefonnummer
• Telefon: 73 59 75 22 (kontor) / 46 85 62 67 (mobil)

Dissertations at the Faculty of Medicine, NTNU

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71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
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73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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