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Fetal programming and its relevance to the obesity and diabetes pandemic in Sri Lanka

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Article Information

The author declares no competing interest.

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Introduction

Obesity is defined as excessive deposition of body fat to a level that is harmful for health, and occurs when the body's energy intake exceeds energy expenditure over a considerable time period. Obesity has multiple medical and psychosocial consequences in childhood as well as adulthood, including type 2 diabetes, and other non-communicable diseases including ischemic heart disease, hypertension, non-alcoholic steatohepatitis, obstructive sleep apnoea, polycystic ovarian syndrome, asthma and cancer, as well as impaired quality of life.

Obesity and type 2 diabetes rates have risen dramatically globally over the past three to four decades, with the recent COVID-19 pandemic worsening the situation. Obesity rates in low- and middle-income countries in the Asia Pacific region including Sri Lanka, have worsened during the past two decades (1).

Sri Lanka had the fourth highest rate of increase in obesity in the region between 2010- 2016, with adult obesity rates increasing by 80% and childhood obesity rates by 40% (1). Type 2 diabetes rates are also rising rapidly in the South Asian region, and occurring at a younger age than elsewhere in the world. A recent community survey among 5-18 year olds in 2019 in the Western Province of Sri Lanka showed high rates of childhood and adolescent overweight (11.3%), obesity (10.3%), and pre-diabetes (impaired fasting glucose levels in 11.2%, and impaired glucose tolerance in 4.3%) (2). Further, a high prevalence of obesity–related metabolic complications, including steatohepatitis, dyslipidaemia and dysglycaemia, was found among Sri Lankan children aged 5-15 year old referred to the University paediatric obesity clinic, Lady Ridgeway Hospital for children, Colombo, Sri Lanka with more than 50% having at least one complication, and a third having two or more complications (3). Notably, the girls had higher rates of insulin resistance, dysglycaemia, dyslipidaemia and higher blood pressure compared to boys even after adjusting for age, birth weight and BMI z score (4). Overweight and obese Sri Lankan children also had lower quality of life (QoL) children compared to age-matched children with normal BMI, with greater impairment of physical QoL noted with increasing BMI (5).

Why is obesity and diabetes increasing ?

The reasons behind obesity are multi-factorial, with complex interactions between genetic, developmental, behavioural, and environmental influences (6). Obesity is widely attributed to an unhealthy lifestyle with unhealthy diet and inadequate physical activity. Social conditioning by food and beverage advertising is an important factor driving unhealthy eating habits among the younger generation. This has been documented among Sri Lankan children as well (7). However, as body weight, appetite and energy balance are regulated by biological systems established in early life, the occurrence of obesity indicates failure of these biological systems, and cannot be explained purely by social determinants (6).

Furthermore, obesity is difficult to reverse, even with intense lifestyle counselling, medical therapy and long term follow up (8, 9). Between 2017-2019, we evaluated the effectiveness of lifestyle advice and regular follow-up, on reducing adiposity among overweight and obese 5-16 year olds presenting to the University Paediatric obesity clinic. Mean body fat (40% at baseline) reduced by 1.4 % over the initial 6 months, and remained similar to baseline levels at 2-year follow up (8,10).

The fetal programming or 'developmental origins of health and disease' concept acknowledges early life environmental during sensitive periods of development including in-utero life, influences one's life-long health. First described in relation to maternal undernutrition in the late 1980s, by David Barker *et al* who showed those humans exposed to undernutrition in-utero had higher risk of developing central obesity, diabetes, hypertension, and cardiovascular disease in adulthood, recent evidence shows that fetal over-nutrition is also associated with a higher risk of obesity in childhood and adulthood (11). In-utero environments that are nutritionally limited and nutritionally excessive are harmful to the fetus, with trouble at both ends of the maternal nutrition spectrum, with a 'J' shaped curve depicting the association between birth weight and future obesity risk. It is proposed that the fetus 'senses' its future nutritional status via *in-utero* signals, and responds in ways which lead to lasting influences on weight and appetite control. Fetal programming is now acknowledged as a major propagator of obesity. Maternal undernutrition, overweight or obesity, and excessive gestational weight gain, as well as certain paternal factors thus adversely impact long term offspring's risk of obesity, diabetes and cardiovascular diseases (11).

Concurrent with the global epidemic of obesity, overweight and obesity has increased among women of reproductive age (12). When considering Sri Lanka, over nutrition (overweight and obesity) rates are now higher than undernutrition rates among women of reproductive age in both urban and rural areas (13). However, a third of plantation sector women remain undernourished aptly depicting the double burden of malnutrition in Sri Lanka (13).

Maternal obesity and offspring health

Fetal exposure to an abnormal metabolic milieu associated with maternal obesity leads to dysregulation of the offspring adipo-insular axis (leptin and insulin) causing alterations in the central nervous system regulation of appetite, activity level, energy balance and adipocyte metabolism (11,14). While we cannot easily discern out effects of fetal programming from genetic and nurturing influences in humans, animal models provide evidence that prenatal exposure to an adverse in utero environment results in epigenetic modifications that lead to lasting changes in appetite and behaviour. Alteration in the gut microbiome associated with maternal obesity have also been implicated in increased risk of the offspring for obesity. Research on epigenetics and the gut microbiome could yield greater insight regarding mechanistic pathways as well as methods of modulating fetal programming in the future (6,11).

Notably, there is some evidence that adverse fetal programming in humans can be altered or prevented by early intervention. Studies in sibling offspring, conceived before and after substantial maternal weight loss from bariatric surgery, showed that offspring conceived after maternal weight loss with bariatric surgery had lower birthweight, better insulin sensitivity and healthier lipid profiles, and lower risk of obesity compared to their siblings conceived prior to bariatric surgery (15). More feasible community wide interventions are now necessary however to improve long term offspring outcomes for the rapidly increasing number of women who become pregnant while being overweight or obese.

Can antenatal exercise help prevent adverse fetal programming?

Fetal programming targets the earliest stages of development of obesity, and provides a novel paradigm to complement other strategies for lifelong prevention of obesity. 'Exercise' refers to any physical activity carried out with the purpose of maintaining or improving health and fitness, and its benefits especially on metabolic health are well documented. While mild to moderate-intensity antenatal exercise in healthy women does not cause any observable harm to the fetus, there is a paucity of data on the effects of antenatal exercise on short- and long-term outcomes in overweight and obese women and their offspring (12).

The IMPROVE (Improving Maternal and Progeny Risks of Obesity Via Exercise) randomised controlled clinical trial was conducted in Auckland, New Zealand, among a multi-ethnic group of non-smoking overweight and obese pregnant women (BMI $\geq$25 kg/m^2) aged 18–40 years with singleton pregnancies, to explore effects of moderate intensity non-weight bearing antenatal exercise on maternal and offspring outcomes including birthweight, body composition, and metabolic markers. We hypothesized that antenatal exercise in overweight or obese women would improve the maternal metabolic milieu, reduce offspring birthweight and improve offspring outcomes protecting them from future obesity and diabetes (14). The trial was registered in the Australian New Zealand Clinical Trials Registry, and ethics approval obtained from the Health and Disability Ethics Committee, New Zealand. Participants were

recruited from the community and randomized to intervention/control groups stratified on ethnicity and parity, by 20 weeks of gestation.

A home-based non-weight bearing antenatal exercise intervention

Intervention participants participated in a home-based structured 16-week moderate-intensity exercise on stationary cycles, from 20 weeks of gestation. Each participant in the intervention group was provided with a magnetic stationary bicycle (Sportop NB600/NB800) to keep at home, and a heart rate monitor (Polar S625/Polar RS800; Polar Electro Oy, Kempele, Finland) to wear during all cycling sessions to maintain prescribed target heart rate and monitor compliance with the intervention. Exercise intensity was prescribed using target heart rate zones developed and validated for overweight and obese pregnant women to maintain exercise sessions at moderate intensity (40–59% VO_2 reserve). Each exercise session including a 5-minute warm-up period of low-intensity cycling, moderate-intensity cycling for 15 - 30 minutes (according to stage of pregnancy) and a 5 minute low-intensity cool-down period. A written programme prescribing frequency and duration of weekly exercise was provided, together with advice by an exercise physiologist. Compliance to the prescribed exercise protocol by each participant was monitored by data downloaded from each heart-rate monitor at the end of the intervention period. The control group was not prescribed any exercise intervention, nor given bicycles or heart rate monitors. Both groups were requested to carry out their routine physical activities.

Monitoring participant fitness, lifestyle, and fetal growth during pregnancy

Maternal submaximal aerobic-capacity and serum metabolic markers were assessed at baseline (19 weeks of gestation) and again at the end-of-intervention period (36 weeks of gestation) (Figure 1). Aerobic fitness testing was carried out using a sub-maximal graded exercise test on an electronically-braked cycle ergometer (Schiller, Baar, Switzerland), with simultaneous breath-by-breath measurement of expired and inspired O2 and CO2 gas volumes (ParvoMedics TrueOne 2400 Metabolic Measurement System, Parvomedics, Sandy, Utah, USA) to a target heart rate of 150 beats per minute. The test began with a workload of 30 W and increased by 10 W every minute until a target heart rate of 150 beats per minute was reached. Participants were instructed to maintain a constant cycling speed at 60 rpm throughout the test. Main parameter assessed was time taken to reach target heart rate of 150 bpm, with longer time duration indicating better fitness (12, 14).

Both exercise and control groups completed diet-records and physical-activity questionnaires at baseline and mid-intervention. Participants also underwent serial fetal ultrasound scans (USS) 4 weekly from 24 weeks of gestation including 3D limb volume data sets to measure limb circumference and partial limb volume of the thigh and upper arm. Both groups received standard antenatal care.

Study outcomes

Offspring assessments included cord blood metabolic markers, birth anthropometry and neonatal body composition (whole-body DXA scanning), while maternal outcomes included weight gain, pregnancy and delivery complications, and post-partum body composition assessment (14,16). Primary outcome was birth weight assessed as standardized z-score (adjusted for gestational age and gender) as well based on customised birth weight centiles (adjusting for maternal height, weight, parity, ethnic origin, gestational age and gender).

The study participants

A total of 195 women were referred by community midwives or through self-referral and were assessed for eligibility to join the study (Figure 2). Seventy-five pregnant women, with a mean age of 31 years and a mean BMI of 33 kgm^{-2} participated in the study (intervention n=38, control n= 37). Both groups had similar aerobic fitness, metabolic markers, dietary-intake and habitual-physical-activity levels at baseline. Dietary-intake and habitual-physical-activity remained similar between exercisers and controls during the intervention-period. Intervention participants completed 33% of prescribed exercise sessions on average, based on downloaded heart rate monitor data. Exercise compliance was especially low towards the latter part of pregnancy (after the 32 weeks of gestation).

Maternal outcomes

Exercise participants improved their fitness levels during the intervention period, and achieved higher aerobic fitness compared to controls by the end-of-intervention period (adjusted mean difference in test-time 48s, P=0.02). However, there was no significant difference in weight gain during the intervention period as well as total gestational weight gain. Maternal serum and plasma metabolic markers of glucose homeostasis and insulin resistance, lipid levels and adipocytokines were also similar between the two groups. Further, there was no differences between groups in pregnancy and delivery outcomes and postpartum body composition (17).

Offspring outcomes

Offspring birth anthropometry including birthweight, as well as serial fetal growth measures on ultrasound scan, and customized birth weight centiles (52 ± 33% vs 43 ± 26%, p=0.12) were similar between intervention and control groups. There was one perinatal death in each group due to reasons unrelated to the exercise intervention. Other birth outcomes were also similar between the two groups. When considering neonatal body composition, offspring in the two groups had similar lean mass and adiposity and, including regional fat distribution (percentage of fat in trunk and

limbs). However, offspring in the exercise intervention had increased bone mineral mass compared to controls (aMD=9.1 g; p=0.010). Cord blood analysed in 56 term offspring (intervention n=25, control n=31), showed a significant reduction in IL-6 levels in offspring whose mothers had undertaken the exercise intervention in pregnancy compared to controls (4.4 vs 19.0 pg/ml, p=0.03), while other metabolic markers, were similar between groups (17).

have been the cause for lack of significant alterations in maternal metabolism, offspring birthweight and adiposity. While the amount of exercise undertaken led to significantly improved maternal fitness among the exercise group, the relatively short time duration (16 weeks) over which the intervention was conducted, combined with poor compliance probably contributed to lack of significant improvement in clinical and metabolic outcomes in both mothers and offspring. Furthermore, the study participants were healthy overweight or obese pregnant women who

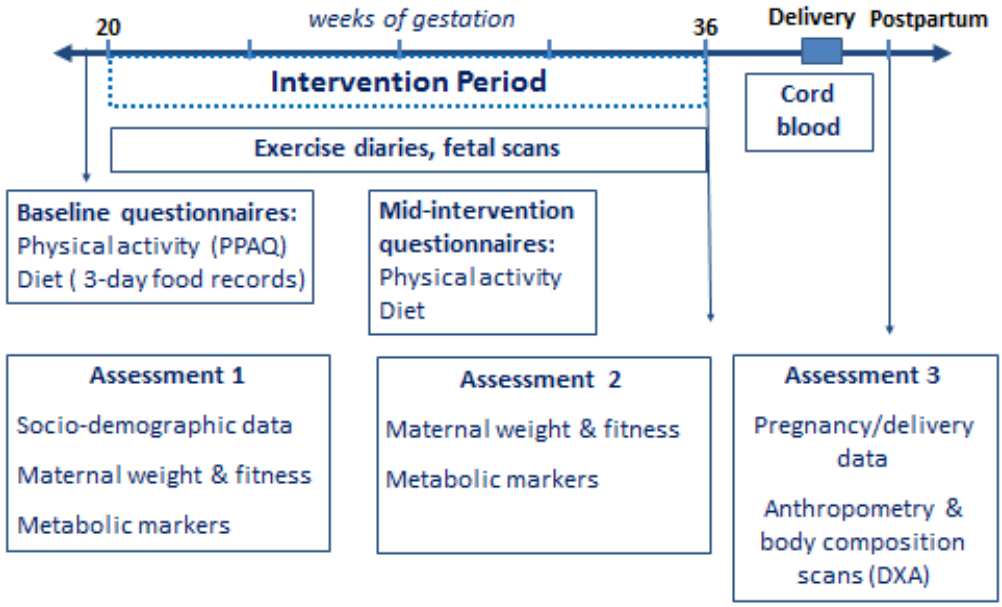

Figure 1 - IMPROVE randomised controlled clinical trial: timeline and assessment points

Did antenatal exercise make any difference?

We did not observe any significant differences in maternal weight gain, maternal metabolic markers, and offspring birth birthweight and adiposity between exercise and control group offspring, to suggest that the intervention had led to positive change in offspring obesity risk. On the positive side however, maternal fitness levels improved, and no adverse clinical effects from antenatal exercise were observed on both maternal and offspring outcomes. Further, though antenatal exercise did not appear to offer much promise for preventing fetal programming of obesity, we observed some exciting secondary findings including a promising effect on offspring bone health, and sex-specific differences in offspring body composition and metabolic profiles between the two offspring groups. These findings offer exciting new avenues for future research (18-20).

Why can't antenatal exercise protect offspring from obesity?

We propose that suboptimal exercise compliance could

volunteered to join this antenatal exercise study willingly, and precautions were taken to help improve compliance by using a carefully designed, home-based, non-weight bearing exercise intervention. It appears unlikely that overweight or obese pregnant women in the community would be able to achieve higher exercise levels. Therefore, it appears unlikely that antenatal exercise *per se* would be sufficient to prevent adverse fetal programming in offspring of overweight/obese women (6).

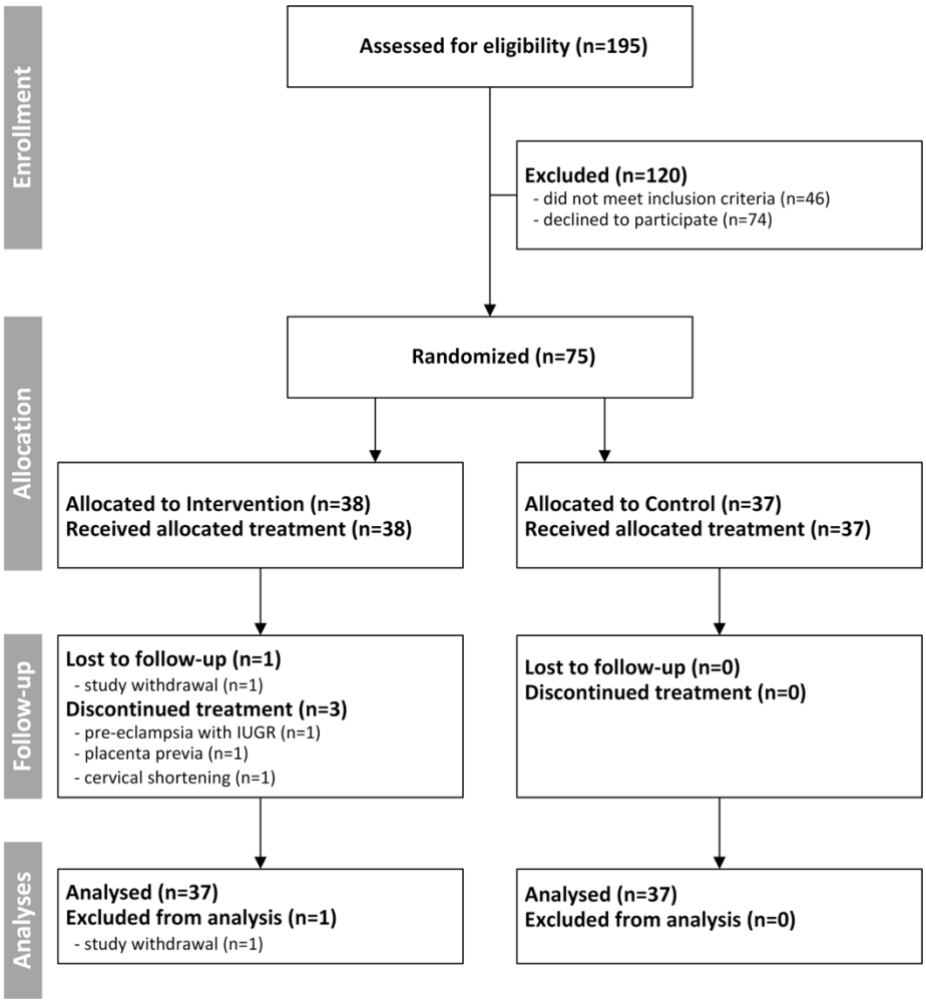

Figure 2- CONSORT diagram describing flow of participants in the IMPROVE study

Effects of antenatal exercise on offspring bone and metabolic health

IL-6 is an inhibitor of early life bone formation, and higher bone mass in early life signifies reduced osteoporosis risk. Exercise intervention group offspring had lower cord blood IL-6 levels as well as greater bone mass of similar mineral bone density compared to control group offspring. To our knowledge, this is the first clinical study reporting association of antenatal exercise with lower fetal IL-6 levels and increased early life bone mass. These findings suggest the potential of antenatal exercise for improving offspring long-term bone health (18). Furthermore, fetal IL-6 levels have also been implicated in fetal programming of insulin-resistance and hypertension in animal models. Thus, long term follow-up of this cohort of offspring of overweight and obese women is important to determine long-term effects from antenatal exercise on bone and metabolic health of offspring.

Sex-specific changes of antenatal exercise on offspring body composition and metabolism

Interestingly, we found sex-specific differences in the offspring body composition and metabolic profiles between the two offspring groups, as well as significant differences in blood glucose and hs-CRP concentrations in pregnant women carrying boys compared to those carrying girls at both mid gestation, and late gestation. This indicates that the sex of the fetus influences maternal metabolism, which may in turn be associated with gender-specific fetal programming on long term health (19, 21).

Mitigating effects of fetal programming: What can we do?

The increase in obesity especially among the younger generation is a worrying trend compounded by the fact that there are no proven strategies for preventing or reversing obesity in childhood. Recognising the importance of fetal programming, the World Health Organisation now advocates a life-course approach to control obesity and diabetes in future generations, starting with pre-conceptional and antenatal health. As interventions to reduce weight or limit weight gain during pregnancy have not met with much success in improving long term offspring outcomes, shifting the focus to optimizing the nutritional status of adolescent girls and women of reproductive age before they embark on pregnancy is the best way forward. This will require an

integrated approach to raise awareness on pregnancy prevention, planning, and preparation, and the importance of good health in the period before pregnancy, which are acceptable for the community within their societal and cultural norms. Further, while the health of adolescents and youth are often viewed as a low priority, it is important and timely to recognise the importance of educating and motivating young people to adopt a healthier lifestyle to improve not only their own health, but also that of the future generation.

A holistic life-course approach focusing on maternal health, antenatal and postnatal care, as well as community-based and targeted healthy-lifestyle interventions for pre-schoolers, school children, and young adults of reproductive age is necessary to break the vicious cycle of obesity and type 2 diabetes in Sri Lanka, and world over. We postulate that South Asian populations such as Sri Lanka, which are undergoing rapid nutritional transitions, are now facing a rapid increase in obesity due to adverse fetal programming from both maternal over- and under-nutrition. High rate of metabolic complications among overweight and obese Sri Lankan adolescent girls is especially concerning, due to the impact of the health of the girl-child on the future generation (4). School-based interventions to encourage a healthy eating habits and lifestyle from a young age, have shown promising results in Sri Lanka, and should be encouraged (22,23). Furthermore, epidemiological studies to identify risk factors for obesity and type 2 diabetes, including fetal programming as well as social conditioning and community based obesity prevention programs are urgently needed to curtail the increasing trend of obesity and diabetes we are facing.

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