Impact of pre-conception weight loss on fasting glucose and pregnancy outcomes in women with obesity: A randomized trial

Price S (FRACP, PhD)\textsuperscript{1,2}, Sumithran P (FRACP, PhD)\textsuperscript{1,3}, Nankervis A (FRACP, MD)\textsuperscript{2,4}, Permezel M (FRANZCOG, MD)\textsuperscript{5}, Prendergast L (B Sc., PhD)\textsuperscript{6}, Proietto J (FRACP, PhD)\textsuperscript{1,3}.

Author affiliation and addresses:

1) Department of Medicine (Austin Health), University of Melbourne, Waterdale Rd, Heidelberg Heights, Victoria, Australia 3081
2) Department of Diabetes and Endocrinology Royal Melbourne Hospital Grattan St, Parkville, Victoria, Australia 3010
3) Department of Endocrinology Austin Health Waterdale Rd, Heidelberg Heights, Victoria, Australia 3081
4) Department of Obstetrics and Gynaecology Royal Women’s Hospital Flemington Rd, North Melbourne Victoria, Australia 3051
5) Department of Obstetrics and Gynaecology

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Corresponding author:
Dr Sarah Price
sarah.price@unimelb.edu.au
+ 61 3 9496 6221

Department of Medicine (Austin Health), University of Melbourne,
Waterdale Rd, Heidelberg Heights,
Victoria, Australia 3081

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Ethics approval:

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This study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614001160628). The study, and all procedures of the study, were approved by Melbourne Health Human Research Ethics Committee on 6th June 2014 (HREC/14/MH/71). Site specific approval at all sites was approved by 5th November 2014. The initial patient was enrolled on 6th November 2014. The final subject was enrolled on 7th February 2018. All subject had completed the study on 30th September 2019.

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Study importance questions
What is already known about this subject?
1. Obesity negatively impacts pregnancy outcomes. This has both short- and long-term consequences for mother and offspring.
2. The current standard of care for the management of obesity prior to pregnancy is lifestyle modification. Bariatric-surgery-induced weight loss reduces maternal adverse pregnancy outcomes but may increase offspring adverse outcomes.
3. In women with obesity planning pregnancy, the impact of non-surgical substantial weight loss on pregnancy outcomes is largely unknown.
What are the new findings in your manuscript?
1. Use of a very low energy diet prior to pregnancy is efficacious and acceptable to women with obesity planning pregnancy.
2. Substantial weight loss achieved using a very low energy diet does not alter fasting glucose at 26-28 weeks gestation but may alter post-prandial glucose control.
3. In a small cohort, substantial weight loss achieved using a very low energy diet significantly reduced a composite of obesity related adverse pregnancy outcomes in both mothers and offspring.

How might your results change the direction of research or the focus of clinical practice?
1. Preconception weight loss studies, while difficult, are critical in ensuring evidence-based care for women with obesity planning pregnancy.
2. Mechanistic studies are required to understand how weight loss may improve pregnancy outcomes. This study suggests post-prandial glucose control should be considered.
3. This study suggests that substantial pre-pregnancy weight loss can reduce obesity-related adverse pregnancy outcomes. Larger RCTs are required to validate this finding.

Abstract

Objective: To examine the effectiveness of a non-surgical pre-conception weight loss intervention on pregnancy outcomes in women with obesity.

Methods: This was a two-arm, parallel-group randomized controlled trial. 164 women with BMI 30–55 kg/m², aged 18-38 years and planning pregnancy were randomized to a 12-week standard dietary intervention (SDI; n=79) or modified very low energy diet (VLED; n=85). Subjects were observed for ≤ 48 weeks while trying for pregnancy, and during pregnancy. The primary outcome was maternal fasting plasma glucose at 26-28 weeks’ gestation. Exploratory outcomes were individual and composite obesity-related adverse pregnancy outcomes.

Results: Weight loss was greater in the VLED group (SDI 3·2±0·6kg vs VLED 13·0±0·5kg, p<0·01). In completers who had a singleton live birth (SDI 22/79 vs VLED 35/85; p=0.10), there was no difference in fasting glucose at 26-28 weeks’ gestation (SDI 4·8±0·2mmol/L vs
VLED $4.6\pm 0.1 \text{mmol/L}, \ p=0.42)$. However, the composite of adverse pregnancy outcomes was significantly lower in the VLED group ($p<0.001$).

**Conclusions:** Substantial pre-pregnancy weight loss in women with obesity does not alter fasting glucose at 26-28 weeks’ gestation but does reduce a composite of adverse pregnancy outcomes. Better understanding of metabolic changes in pregnancy after pre-conception weight loss may assist us to improve maternal and neonatal health outcomes.

**Introduction**

The strong and continuous association between increasing body mass index (BMI) and adverse pregnancy outcomes is well documented (1, 2). It is also widely appreciated that the early metabolic environment of the offspring influences the susceptibility to metabolic disease later in life (3, 4, 5). Given that maternal obesity is independently associated with offspring adiposity (3, 6), addressing obesity in women planning pregnancy is of critical importance.

Guidelines from multiple countries recommend women with obesity should institute lifestyle change, comprising an energy-reduced diet and increased physical activity, prior to pregnancy (7). This typically results in modest weight loss ($<3\%$ body weight) which may improve fertility but does not impact pregnancy outcomes (8, 9).

Retrospective studies suggest that substantial weight loss ($>10-15\%$ body weight), achieved with bariatric surgery, reduces the rate of adverse pregnancy outcomes for the mother (10). However, surgery-induced weight loss may have deleterious consequences for the offspring with an increased rate of small for gestational age offspring and possibly increased offspring mortality (10, 11).

Very low energy diets (VLEDs) can also induce substantial weight loss ($10-15\%$ weight loss over 8-12 weeks) in persons with obesity (12). However, the impact of use in the pre-pregnancy setting and on pregnancy outcomes is unknown.

The objective of this study was to determine if non-surgical substantial weight loss can be achieved in women with obesity prior to pregnancy using a modified VLED program, and to determine whether this weight loss improves glucose metabolism and obesity-related adverse pregnancy outcomes for both mother and offspring.
Methods

Study design and participants

This was a two-arm, parallel group, randomized controlled trial. Using a social media platform, we recruited women with a body-mass index (BMI, weight in kilograms divided by the square of the height in meters) between 30-55 kg/m$^2$ who were planning pregnancy within 6-12 months. The study was conducted in two tertiary adult hospitals and two tertiary maternity hospitals in Melbourne, Australia.

Persons who were pregnant, with known irreversible infertility, diabetes, significant medical illnesses, and those taking medication known to affect weight were excluded. Women with known polycystic ovarian syndrome (PCOS), as defined by the Endocrine Society clinical practice guideline, were included in the study regardless of their ovulatory status (13). A stable dose of metformin was permitted. Women who required assisted reproductive treatment were not excluded provided that all procedures including harvesting of oocytes occurred after the study intervention.

Primary and exploratory outcomes were based on the first conceived singleton pregnancy during the observation period (Wk 13-60). Pregnancies that occurred during the intervention (Wk 0-12) and multifetal pregnancies were excluded from analyses, but pregnancy outcome data were collected (Supplementary Data).

The study was prospectively registered (ACTRN12614001160628) and was approved by the Human Research Ethics Committee at participating institutions. All participants provided written consent.

Randomization

Women were randomized to one of the two treatment arms (SDI or VLED) using computer-generated randomly permuted blocks of size 2, 4 or 6 (also randomly chosen) within 6 strata accounting for BMI (30–34·9; and 35–55 kg/m$^2$), age (18–29 and 30–38 years), and parity (0 or 1+). A research assistant not involved with the study held the randomization list and allocated participants to treatment groups. Investigators, other than the study statistician, did not have access to the randomization list. All study visits were conducted by qualified
research staff with investigator over-sight. Treatment group allocation was unmasked to all persons involved with the study.

Procedures
The study occurred in three phases (Figure S1) and is described in detail in the published protocol (14). Study visits were conducted as individual, face-to-face consultations at a Melbourne based tertiary hospital.

At study enrolment, subjects were asked to use medically proven forms of contraception until the completion of the weight maintenance phase. As per local pre-pregnancy guidelines, subjects commenced folate (5mg PO daily) and a multivitamin containing 150 µg iodine, and were asked to continue these medications until at least 12 weeks of pregnancy.

Weight-Loss Phase (Phase 1; Wk 0-12)
For 12 weeks, subjects were seen fortnightly. The first and final visits (Wk 0 and 12) were 1-hour and intervening visits were 30-minutes. Weight, bioimpedance, blood ketones and a urine pregnancy test were performed at each study visit. All participants wore a pedometer (Yamax 700S) for a minimum of 7 consecutive days (Wk 2) and aimed for >10,000 steps per day.

The SDI group were instructed to eat an energy reduced diet. A dietician calculated current caloric intake and recommended a diet containing 500 fewer calories per day than the current intake. Dietary recommendations were made based on the ‘Australian Dietary Guidelines’(15). Meals were not provided.

The VLED group were instructed to eat a modified VLED consisting of two daily meals of a very-low-energy dietary formulation (Optifast VLCD, Nestlé®) and to eat a third meal consisting of 2 cups of low-starch vegetables, 150g lean meat, fish, eggs or tofu, and 2 teaspoons of oil (14). Total daily calorie intake was approximately 800 calories. The VLED product was provided but other components of the diet were not.

At the end of week 12, all participants received individual counselling from a dietician on a dietary intake required to maintain weight based on the calculated energy expenditure (as calculated by the Harris-Benedict equation). Macronutrient composition was not prescribed.
Weight Maintenance Phase (Phase 2: Wk 13-16)
This phase was intended to allow wash-out of ketosis and to stabilize body weight in preparation for conception (16). At the end of week 16, weight, bioimpedance, blood ketones and a urine pregnancy test were performed. Subjects received 1-hour dietary counselling to assist weight maintenance.

Pre-pregnancy Phase (Phase 3a: Wk 17-60 Pre-pregnancy)
In the pre-pregnancy phase, subjects were invited to 30-minute study visits every 12 weeks. A urine pregnancy test was performed, and dietary counselling was provided to assist weight maintenance. Participants were advised to remain physically active (>10,000 steps/day). If a phone visit was preferred in this phase, dietary counselling was provided by phone, weight was recorded using home scales, and a home pregnancy test was performed.

Pregnancy Phase (Phase 3b: Pregnancy)
Participants advised the study site if a home pregnancy test was positive. Medical and obstetric data were collected throughout pregnancy. Maternal and neonatal outcome data were taken from the birth discharge summary. This information was documented by the attending midwife and/or obstetrician; these persons were not related to the study. Outstanding data were collected from the paper-based medical record by the study coordinator.

Data collection
Study visits were performed between 08:00 and 10:00hr in the fasting state. Anthropometric measurements were taken barefoot in light clothing. Participants were weighed using calibrated digital scales. Body composition was measured by bioelectrical impedance (TBF-300, Tanita, WW Wedderburn Pty, Sydney, Australia).

Biochemical assays
The primary outcome was fasting glucose on the 75g oral glucose tolerance test (OGTT) performed at 26–28 weeks’ gestation. This is part of standard maternity care in Australia and ensured the largest number of samples for analysis. Storage and processing of samples occurred according to a standard protocol. Testing was performed using one of two
enzymatic methods: glucose oxidase or hexokinase. Although samples were processed in different laboratories, inter-assay variation is expected to be very low (17). Both glucose assays meet the 1992 National Institute of Health goal of ≤3% for precision and bias.

Outcomes
The primary outcome was the maternal fasting plasma glucose at 26-28 weeks’ gestation on the 75g Oral Glucose Tolerance Test. We hypothesized that a 12-week pre-conception VLED program would induce substantial weight loss (10-15% body weight) which would reduce maternal fasting plasma glucose at 26-28 weeks’ gestation by 10% when compared with women prescribed the SDI (3% weight loss). Further, weight loss would improve pregnancy outcomes.

Adverse pregnancy outcomes related to obesity have previously been identified in published literature (1). Based on these, pre-specified exploratory outcomes were a reduction in (1) gestational diabetes (International Association of the Diabetes and Pregnancy Study Group criteria maternal fasting glucose ≥ 5·1 mmol/L, 1-hr glucose ≥ 10·0 mmol/L, 2-hr glucose ≥ 8·5 mmol/L), (2) gestational hypertension/pre-eclampsia (systolic blood pressure >140mmHg and/or diastolic blood pressure >90mmHg or pre-eclampsia identified after 20 weeks gestation), (3) delivery <37+0 weeks’ gestation, (4) primary Caesarean section (the first Caesarean section performed on a woman, regardless of indication), (5) shoulder dystocia/birth injury, (6) large-for-gestational-age offspring (birth weight >90% centile, adjusted for gestational age and sex), (7) intra-uterine-growth-restriction (birth weight <10% centile adjusted for gestational age and sex because of a pathological process), (8) neonatal hypoglycemia (glucose ≤ 2·6 mmol/L), (9) neonatal hyperbilirubinemia (excess total serum bilirubin based on a nomogram that takes into account neonatal gestation, age and birth weight), (10) neonatal special care nursery (SCN)/ intensive care unit (ICU) admission (excluding admission for aforementioned events), and (11) a composite outcome of all of the above. Data regarding time to pregnancy has been published (13). Findings of the epigenetics sub-study will be reported in a subsequent publication.

Statistical Analysis
We estimated that a sample size of 164 women would have 80% statistical power (two tailed 0·05) to detect a 10% relative reduction in fasting plasma glucose at 26-28 weeks’ gestation,
allowing for 40% attrition due to non-completion of the intervention, failure to conceive in the observation period, or early pregnancy loss.

Subjects who completed the 12-week intervention as per protocol were defined as ‘completers’ and those not completing the 12-week intervention were defined as ‘non-completers’. Providing the subject did not withdraw from the study, both ‘completers’ and ‘non-completers’ were followed until the end of the first documented pregnancy (miscarriage or birth) or the end of study visit. In subjects who withdrew, no further data were collected but data already collected were included in the analysis.

As per our priori statistical plan, a completer only analysis was carried out and this was supported by an intention to treat (ITT) analysis. For the weight data, completer only analysis included completers of the 12-week weight loss intervention. We conducted the completers only analysis to directly investigate the association between the pre-pregnancy weight loss intervention and pregnancy outcomes. Weight changes in the intervention period were modelled using linear mixed effects models to account for the repeated measures and an ITT analysis was carried out using multiple imputation. This analysis included all subjects regardless of whether they completed the intervention. Multiple imputation analysis was carried out on 5 datasets generated using multivariate chained equations with the R MICE package (18) to account for missing visits where weight was missing. For the birth outcomes, the completers only analysis included all subjects who completed the 12-week weight loss intervention and had a live birth. The ITT analysis for birth outcome included all subjects who had a live birth regardless of whether they completed the intervention or complied with the study protocol. In the ITT analysis, outcomes for those who did not complete the 12-week weight loss intervention were obtained via follow-up as per the study protocol. Comparisons between groups for continuous data were conducted using the Mann-Whitney U test. Comparisons between groups for categorical data were conducted using Fisher’s exact test. Post hoc outcomes were clearly identified.

A priori decision was made to present pregnancy outcome data without adjustment for co-variates given that adjustment for many co-variates in a small cohort can lead to over-adjustment bias. Exclusions were applied to prevent causally linked adverse pregnancy events being counted twice in the composite outcome. For example, because both
hypoglycemia and SCN admission were events included in the composite outcome, SCN admission for hypoglycemia would be counted as one event rather than two events.

Due to the small event counts relative to sample sizes, we used Fisher's exact test to compare the two groups and the reported the corresponding p-values. A conditional Maximum Likelihood Estimate of the OR, as well as a confidence interval for the OR, were also reported. Comparisons between groups for number of adverse outcomes were conducted using a negative binomial generalized linear regression model to allow for overdispersion in the counts. The regression model was fitted using the MASS package in the R statistical software (19). Confidence intervals for differences in quantiles were obtained using standard errors calculated using the quantile optimality ratios method (20).

Results
Baseline characteristics of all participants who commenced the study are shown in Table 1. There were no significant differences in any baseline measurements between those randomized to the standard dietary intervention (SDI) and the very low energy diet (VLED).

Among the 164 women recruited, 35 were non-completers of the 12-week intervention (SDI n=25/79 (32%), VLED n=10/85 (12%)) and were excluded from the completers only analysis (Figure 1 and Table 2). The only significant difference between completers and non-completers was a higher body weight in non-completers than completers of the SDI group (Table S1).

Despite advice to use contraception, five women achieved pregnancy during the weight loss intervention (SDI n=1/79 (1%), VLED n=4/85 (5%), p=0.37) and were excluded from the completers only analysis. Pregnancy outcomes of these subjects are outlined in Table S2. Forty-two women completed the intervention but did not achieve a pregnancy during the observation period (SDI= 21/79 (27%), VLED n=21/85 (25%), p=0.85).

As previously published (13), in completers of the intervention who became pregnant, the median time to pregnancy (first quartile, third quartile) in the SDI group was 140.5 days (75.3 days, 211.0 days) and VLED group was 51.0 days (32.0 days, 169.0 days).
Spontaneous pregnancy loss at <12 weeks’ gestation occurred in 23 women (SDI n=10/79 (13%), VLED n=13/85 (15%), p=0.66). 59 subjects achieved a pregnancy (n=57 singleton, n=2 multifetal gestation) resulting in a live birth during the observation period (SDI n=22/79 (28%), VLED n=37/85 (44%), p=0.05) (Table 2 and Table S3).

**Weight Loss**

During the 12-week intervention, and including all participants irrespective of eventual pregnancy, weight loss was significantly greater in the VLED group at all time points after Week 2 (Figure 2a, all p < 0.001). At Week 12, the average difference in weight loss between the SDI and VLED groups was 9.8kg (95% CI 8.8 to 10.7; ITT 9.2kg 95% CI 7.6 to 10.8) with a 3.2kg loss in the SDI group (95% CI 2.5 to 3.9; ITT 2.1kg 95% CI 1.1 to 3.1) and 13.0kg in the VLED group (95% CI 12.4 to 13.6; ITT 11.2kg 95% CI 9.4 to 13.1). Changes in other anthropometric data for those who completed the weight loss intervention are shown in Table S4.

**Weight change prior to pregnancy/end of study visit**

The maximum trial duration was 60 weeks plus the duration of pregnancy. After completion of the 12-week intervention, subjects tried for pregnancy over a maximum 48-week observation period. In completers of the intervention, weight change in the pre-pregnancy observation period (defined as the period between the end of the 12-week intervention and either 12 weeks’ pregnancy or the end of the 48-week observation period in those not achieving pregnancy) was not different between groups (Figure 2b). Weight regain in this period was 3.0 ± 0.7kg (2.9%) in the SDI group and 3.6±0.9kg (3.2%) in the VLED group (p=0.84).

**Gestational Weight Gain**

Pregnancy duration was not different between groups (SDI 269 ± 3 days, VLED 272 ± 2 days, p=0.35). There was also no difference in gestational weight gain, defined as weight change between 12 weeks’ pregnancy and delivery, between groups (SDI 10.9 ± 1.0kg, VLED 10.3 ± 1.0kg, p=0.66).
Primary outcome

All women with a pregnancy resulting in live birth underwent a 75g oral glucose tolerance test (OGTT) between 26+0- and 28+0-weeks’ gestation (Table S5). No subjects were diagnosed with gestational diabetes prior to 26-28 weeks’ gestation. All subjects diagnosed with gestational diabetes on this test were treated according to local guidelines. There was no difference in fasting maternal plasma glucose at 26–28 weeks’ gestation between groups on the OGTT samples (SDI 4·8 ± 0·2 vs VLED 4·6 ± 0·1 mmol/L, p=0·42). This finding is validated by the finding of no difference on fasting glucose samples drawn between 26-28 weeks’ gestation at clinical trial visits (SDI 5.1±0.3 vs VLED 4.9±0.1mmol/L, p=0.67).

Post-hoc analysis of the glucose titer 1-hour post glucose load demonstrated no difference between groups (SDI 7·9 ± 0·42mmol/L, VLED 7·4 ±0·3 mmol/L, p=0·42). However, glucose titer 2-hours post glucose load was significantly higher in women randomized to SDI compared to VLED (SDI 6·7 ± 0·3mmol/L, VLED 5·9 ± 0·2, p=0·04).

The pragmatic decision to include subjects on metformin was made priori because of anticipated difficulties in recruitment. When subjects taking metformin (SDI 2/79, VLED 4/85, p=0.69) were excluded, post-hoc analysis of fasting maternal glucose samples from the OGTT demonstrated no difference between groups (SDI 4·8 ± 0·2 vs VLED 4·6 ± 0·1 mmol/L, p=0·34).

Exploratory Outcomes-Pregnancy Outcomes

Pre-specified exploratory pregnancy outcomes were collected from maternity discharge summaries (Table 3 and Table S7). A statistically significant difference in the composite of obesity-related pregnancy outcomes was found between the SDI and VLED groups (Completer only analysis 38 events in 22 subjects vs 24 events in 35 subjects; p=<0·001; ITT analysis 42 events in 25 subjects vs 40 events in 44 subjects/46 neonates p=0.006).

In completers who became pregnant, the total Caesarean section rate was not different between groups (SDI 8/22; VLED 6/35, p=0.12), nor was the primary Caesarean section rate (p=0.12; Table 3). Reasons for neonatal SCN/ICU admission other than specified in Table 3 included sepsis, meconium aspiration, hypothermia, and respiratory distress syndrome. There was no difference in neonatal SCN/ICU length of stay (SDI 10.3 ±6.5 days vs VLED 6.3 ±
3.4 days, p=0.61). There also was no difference in maternal length of stay (SDI 3.7 ± 0.3 days vs VLED 3.0 ± 0.3 days, p=0.08).

Adjusted birthweight centiles are shown in Figure 3. A significant difference in the third quartile was found (difference 18.5, 95% CI 3.89 – 33.11) indicating larger extremes in the SDI group. Larger birthweight centiles in the SDI group were also suggested (difference in medians 22, 95% CI -1.84 – 45.84).

Discussion

Main Findings

To our knowledge, this is the first prospective randomized controlled trial to explore the impact of pre-pregnancy substantial weight loss using a very low energy diet on pregnancy outcomes in women with obesity who were not specifically seeking pregnancy via assisted reproduction.

Results

A standard dietary intervention prescribed in accordance with current Australian guidelines for women with obesity resulted in modest weight loss (3.2kg) over 12 weeks, consistent with previous lifestyle studies (8, 9, 21). A modified VLED program resulted in substantial weight loss (13.0 kg), consistent with results from studies using the same protocol in a general adult population (22).

Since weight loss brings about compensatory changes in peripheral hormones (22) and energy expenditure (23), some weight regain was expected. Weight regain prior to conception did occur in both groups but was not different between groups (p=0.84). This is consistent with a previous study reporting that the rate of weight loss does not influence the rate of weight regain (12).

In intervention completers who achieved pregnancy, gestational weight gain (GWG) was also not different between groups (p=0.66). This finding is discordant with the PREPARE trial which showed participants in the intervention group gained more GWG than controls (21). However, PREPARE did not have a weight maintenance phase prior to conception. This may suggest a benefit of weight maintenance after a weight loss program.
In a normal pregnancy, insulin resistance progressively increases over the pregnancy, allowing shunting of nutrients to the growing fetus (24). Fasting plasma glucose is generally lower in pregnancy than the non-pregnant state due to increased maternal plasma volume, increased fetal-placental glucose utilization (24), and the feto-placental glucose steal phenomenon (25). This occurs despite increased hepatic glucose production and an increase in insulin resistance of more than 60% over the period of gestation, largely due to the effects of placental-derived factors (26).

Women with obesity who do not have diabetes show greater increases in insulin resistance during pregnancy than women of normal weight who do not have diabetes (27). Previous studies show fasting glucose titers at 26-28 weeks gestation are \( \approx 10\% \) higher in women with obesity than women of normal weight (28, 29). Conversely, weight loss reduces insulin resistance (30). Our pilot data demonstrated that substantial weight loss resulted in an \( \approx 10\% \) decrease in fasting glucose at 26-28 weeks’ gestation (14). These data informed the hypothesis for the primary outcome.

We anticipated that the VLED group would achieve greater pre-conception weight loss, improved insulin sensitivity and a lower fasting glucose at 26-28 weeks’ gestation than the SDI group. However, we found no difference in fasting glucose between groups. This may be because the mechanisms for maintaining normoglycaemia in the fasting state were robust in both groups (Table S6).

Post hoc analysis of the 75g OGTT demonstrated a significantly lower 2-hr post-prandial glucose in the VLED compared to the SDI group. This suggests that pre-conception weight loss improves post prandial glucose clearance either by enhanced insulin secretion and/or by enhanced clearance of plasma glucose by peripheral tissues because of improved insulin action.

Although the RADIAL study demonstrated that pre-conception lifestyle counselling did not reduce the incidence of gestational diabetes (31), both the present study and PREPARE (21) demonstrated a nonsignificant trend towards reduction in gestational diabetes in the study arms achieving greater weight loss. The amount of preconception weight loss may be important in the likelihood of subsequent gestational diabetes.
Given the small sample size, pregnancy outcomes were analyzed as a composite of prespecified obesity-related maternal and neonatal pregnancy outcomes. The VLED group had significantly fewer adverse pregnancy outcomes than the SDI group (completer only analysis \( p<0.001 \), ITT analysis \( p=0.006 \)).

There are several possible explanations for the change in the composite of pregnancy outcomes after preconception weight loss despite the finding of no difference in fasting maternal glucose at 26-28 weeks gestation. Firstly, preconception weight loss may have significantly altered glucose metabolism during other stages of the pregnancy such as the first trimester. Secondly, the difference in the composite of pregnancy outcomes may be explained by weight loss altering the 24-hour AUC glucose or post-prandial glycemic excursions. The concept of mild subclinical hyperglycemia impacting pregnancy outcomes in women with obesity has previously been suggested by Barbour et al. (28) and Harmon et al. (29). Thirdly, weight loss may have improved insulin resistance which then altered the flux of nutrients including glucose (32), fatty acids, and amino acids to the feto-placental unit. (33, 34). It is also possible that preconception weight loss alters pregnancy outcomes by changing metabolic factors that are unrelated to glucose metabolism.

The rate of LGA offspring was of particular interest given the association with long-term metabolic dysregulation (4). Although the study was not specifically powered to detect a difference in the incidence of LGA, fewer LGA offspring were born in the VLED group (SDI \( n=4 \) (18%) vs VLED \( n=0 \) (0%)). The rate of LGA offspring in the SDI group was consistent with the lifestyle arm of the LIMIT study (19%) (35) and other large epidemiological studies (~15%) (1, 36). We would have expected 5-6 LGA neonates in the VLED group; the finding of no LGA offspring is compelling (4, 37).

One of the primary concerns around preconception weight loss is the possibility of increasing the rate of intra-uterine growth restricted (IUGR) neonates (38). Small for gestational age neonates (SGA; \(<10^{th} \) centile) is often used as a proxy for IUGR \(<10^{th} \) centile adjusted for age and sex with a pathological etiology). Our study found no difference in the IUGR rate between groups (Table 3). The PREPARE trial noted a nonsignificant trend towards a higher rate of SGA neonates in the intervention arm (21). Retrospective studies of pregnancy outcomes after bariatric surgery also indicate a significantly higher rate of SGA (8, 10). This may be the direct result of weight loss (39), or because surgery irreversibly alters nutrient absorption from the gut (10). In the present study, despite substantial weight...
loss in the VLED group, there was no increase in the rate of IUGR offspring. This may be because VLED programs do not compromise nutritional status, particularly protein intake, despite calorie restriction (40, 41).

In the SDI group, three neonates (13%) were noted to have major congenital abnormalities (42). This finding was unusual given the reported rate of major congenital abnormalities in women with class II obesity is 4.7% (43). These events did not occur in neonates born with IUGR or LGA. This higher than expected rate of congenital abnormalities may be explained by factors unrelated to obesity. Pediatric review of neonates born with supraventricular tachycardia requiring ablation and laryngomalacia suggested genetic factors and advanced maternal age respectively were the most significant risk factors for the observed congenital anomalies. Unexpectedly, the rate of gestational hypertension/pre-eclampsia was higher in the VLED group. The mechanism for this finding is unclear and will be the subject of future research.

**Strengths and Limitations**

This study has several limitations. The study cohort was relatively small. However, recruitment via social media is thought to give better representation of the general population than other methods of recruitment (44). Power calculations were based on 60% subject retention (98/164). However only 35% (57/164) completed the study as per protocol and had a live birth. The rate of non-completion of the intervention was high, particularly in the SDI group. This may reflect the effectiveness of the weight loss intervention. Also, standard diets increase appetite whereas VLED’s suppress appetite (due to ketosis) (45) which may have improved tolerability of the latter. As expected, not all women achieved pregnancy within the observation period and a proportion of pregnancies ended in spontaneous abortion. This gives rise to the possibility of live-birth bias. As noted previously, pregnancy outcome data were presented without adjustment for co-variates given that adjustment for many co-variates in a small cohort can lead to over-adjustment bias. These points notwithstanding, the study describes a well characterized cohort of women with obesity planning spontaneous conception.

To maximize the number of samples for analysis, the pragmatic decision was made to base the primary outcome on the results of the 75g OGTT collected as part of standard maternity care. Glucose samples were collected and processed in different laboratories, using one of two different assays. Although inter-assay variation is possible, pre-analytic variation is
minimized by a standard protocol for collection and the External Quality Assurance Program (in which all Australian laboratories enroll) reports very small analytic variation for glucose (CV<2.0%).

**Interpretation**

The literature regarding pregnancy outcomes after non-surgical weight loss is sparse (8). Einarsson et al. published one of the few randomized controlled trials exploring the impact of pre-conception weight loss using a VLED program and reported no difference in pregnancy outcomes (46). The discordance between the Einarsson et al. study and the present study with respect to pregnancy outcomes may be explained by the different study cohorts. The Einarsson et al. study population was sub-fertile women (mean 38 months infertility), with a lower BMI at randomization (mean 32.8 kg/m²), who achieved less weight loss in the VLED group (mean 9.4 kg), and women conceived via assisted reproductive treatment (46). The PREPARE study also reported no difference in pregnancy outcomes after a pre-pregnancy behavioral intervention compared with standard care (21). Although the mean BMI of the study population was similar to the present study (mean 36.8 kg/m²), the intervention arm of the study achieved less weight loss than the present study (mean 3.7 kg body weight). The PREPARE study noted more gestational weight gain in the intervention arm of the study which was not observed in the present study (21). This difference may suggest the importance of a weight maintenance phase prior to conception.

**Implications**

Currently, there are no known tools for reducing that rate of both maternal and offspring obesity-related adverse pregnancy outcomes. The present study demonstrates that a preconception VLED program may fill this niche. A VLED program has been shown to be efficacious and acceptable for women with obesity who desire substantial preconception weight loss. Replication of this study in a larger cohort would provide further evidence for the role of VLED programs in achieving weight loss that improves pregnancy outcomes. If the results of this study were replicated in a larger cohort, this tool would be readily translatable to clinical practice.

**Conclusions**

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A VLED program resulting in substantial weight loss did not alter fasting glucose at 26-28 weeks’ gestation but did significantly reduce a composite of obesity-related adverse pregnancy outcomes. This randomized controlled trial is the first to demonstrate that a non-surgical pre-pregnancy weight loss intervention resulting in substantial weight loss can alter obesity-related pregnancy outcomes. Replication of these results in a larger study would confirm that obesity-related adverse pregnancy outcomes can be prevented through a pre-conception weight loss intervention.

Acknowledgements
We are indebted to all the women who participated in this randomized trial and the families who supported them.

Individual participant data that underlie the results reported in this article will be shared after deidentification (text, tables, figures, and appendices). The study protocol has been published. Data sharing will begin 3 months and ending 5 years following article publication to researchers who provide a methodologically sound proposal to achieve the aims in the approved proposal. Proposals should be directed to sarah.price@unimelb.edu.au. To gain access, data requestors will need to sign a data access agreement.

References


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Figures

Figure 1: CONSORT 2010 Flow Diagram

Figure 2a: Intention to treat analysis of body weight change during the weight loss intervention (Phase 1).

Figure 2b: Body weight change in ‘completers’ during the weight loss intervention (Phase 1), weight maintenance period (Phase 2) and pre-pregnancy period (Phase 3a).

Figure 3: Birthweight centiles according to maternal pre-conception weight loss intervention.

Nb. There was a significant difference between the 3rd quartiles of the adjusted birthweight centiles for the SDI and VLED groups (estimated difference 18.5, 95% CI [3.89, 33.10]) with results for the differences in medians also suggesting a difference (difference in medians 22.0, 95% CI [-1.89, 45.84]). The difference in 1st quartiles was insignificant (-.50, 95% CI [-29.88, 28.88]).
Table 1: Baseline characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>SDI</th>
<th>VLED</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomised</td>
<td>79</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Age: years</td>
<td>32·6 ± 3·6</td>
<td>32·1 ± 5·2</td>
<td>0·58</td>
</tr>
<tr>
<td>Caucasian: no. (%</td>
<td>61 (77%)</td>
<td>73 (86%)</td>
<td>0·16</td>
</tr>
<tr>
<td>Education (Tertiary)</td>
<td>44 (56%)</td>
<td>51 (60%)</td>
<td>0·64</td>
</tr>
<tr>
<td>Parity (1+)</td>
<td>20 (25%)</td>
<td>31 (32%)</td>
<td>0·13</td>
</tr>
<tr>
<td>Current smoker: no. (%</td>
<td>5 (6%)</td>
<td>8 (9%)</td>
<td>0·57</td>
</tr>
<tr>
<td>PCOS (%)</td>
<td>30 (38%)</td>
<td>34 (40%)</td>
<td>0·87</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>103·4 ± 2·1</td>
<td>108·3 ± 2·4</td>
<td>0·13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37·9 ± 0·7</td>
<td>39·5 ± 0·7</td>
<td>0·13</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>108·7 ± 1·9</td>
<td>113·2 ± 2·0</td>
<td>0·11</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>121·2 ± 1·6</td>
<td>124·0 ± 1·8</td>
<td>0·21</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>56·5 ± 2·1</td>
<td>60·5 ± 2·1</td>
<td>0·19</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>40·9 ± 0·9</td>
<td>40·3 ± 0·9</td>
<td>0·62</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122·6 ± 1·3</td>
<td>124·0 ± 1·5</td>
<td>0·47</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79·4 ± 1·0</td>
<td>79·9 ± 1·0</td>
<td>0·69</td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>5·4 ±0·1</td>
<td>5·4 ±0·1</td>
<td>0·92</td>
</tr>
</tbody>
</table>

Mean ± 1 SE. Comparisons between groups for continuous data were conducted with the Mann Whitney U test.
Comparison between groups for categorical data were conducted with Fischer’s exact test.

Nb. Detailed methodology for the collection of the baseline characteristics is found in Price et al. Trials, 19(1), 2018.
Table 2: Study outcomes of recruited subjects

<table>
<thead>
<tr>
<th></th>
<th>SDI n=79</th>
<th>VLED n=85</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-completers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pregnancy in non-completers</td>
<td>5</td>
<td>7</td>
<td>0.41</td>
</tr>
<tr>
<td>Pregnant after exit resulting in miscarriage</td>
<td>2</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Pregnant after exit resulting in live birth</td>
<td>2</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>Pregnant in Phase 1 (excluded)</td>
<td>1</td>
<td>4</td>
<td>0.37</td>
</tr>
<tr>
<td>Not pregnant</td>
<td>21</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Completers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pregnancy in completers</td>
<td>32</td>
<td>50</td>
<td>0.03</td>
</tr>
<tr>
<td>Pregnancy resulting in miscarriage</td>
<td>10</td>
<td>13</td>
<td>0.66</td>
</tr>
<tr>
<td>Pregnancy resulting in live birth</td>
<td>22</td>
<td>35</td>
<td>0.10</td>
</tr>
<tr>
<td>Multiple pregnancy (excluded)</td>
<td>0</td>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>Not pregnant</td>
<td>21</td>
<td>21</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Nb. Completers are defined as those subjects who completed the 12-week intervention (Phase 1). Non-completers are defined as those subjects who did not complete the 12-week intervention (Phase 1). Comparison between groups for categorical data were conducted with Fischer’s exact test.
Table 3: Pregnancy outcome data according to maternal pre-conception weight loss intervention

<table>
<thead>
<tr>
<th></th>
<th>Completers Analysis</th>
<th></th>
<th>Intention to treat Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDI (n = 22)</td>
<td>VLED (n = 35)</td>
<td>SDI vs VLED (Completers Analysis; Total Events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDI vs VLED (Completers Analysis; Exclusions applied)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDI (n = 25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VLED (n = 44 mothers, 46 neonates)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDI vs VLED (ITT Analysis; Total Events)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDI vs VLED (ITT Analysis; Exclusions applied)</td>
</tr>
<tr>
<td>Total Exclusions applied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 (45%)</td>
<td>10 (45%)</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes (IADPSG/ADIPS)</td>
<td>10</td>
<td>8 (23%)</td>
<td>8 (23%)</td>
</tr>
<tr>
<td></td>
<td>(45%)</td>
<td>(23%)</td>
<td>(23%)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>0.36 (0.1, 1.31)</td>
<td>0.36 (0.10, 1.31)</td>
<td>0.36 (0.10, 1.31)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Total Exclusions applied</td>
<td>10 (40%)</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Gestational HTN / Pre-eclampsia</td>
<td>3 (14%)</td>
<td>6 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(14%)</td>
<td>(17%)</td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>1.30 (0.24, 9.03)</td>
<td>1.30 (0.24, 9.03)</td>
<td>1.30 (0.24, 9.03)</td>
</tr>
<tr>
<td>p-value</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Total Exclusions applied</td>
<td>3 (12%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes (IADPSG/ADIPS)</td>
<td>9*</td>
<td>9* (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(20%)</td>
<td>(20%)</td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>1.87 (0.41, 11.9)</td>
<td>1.87 (0.41, 11.9)</td>
<td>1.87 (0.41, 11.9)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.52</td>
<td>0.52</td>
<td>0.52</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
<th>Confidence Interval</th>
<th>P Value</th>
<th>Count</th>
<th>Percentage</th>
<th>Confidence Interval</th>
<th>P Value</th>
<th>Count</th>
<th>Percentage</th>
<th>Confidence Interval</th>
<th>P Value</th>
<th>Count</th>
<th>Percentage</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Caesarean section*</td>
<td>8</td>
<td>36%</td>
<td>0.09, 1.48</td>
<td>0.12</td>
<td>10</td>
<td>40%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2^</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Large for gestational age (LGA) (&gt; 90th centile) (Lancaster et al. 1999)</td>
<td>4</td>
<td>18%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>6</td>
<td>24%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2^</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Intra-uterine growth restriction (IUGR) (Lancaster et al. 1999)</td>
<td>3</td>
<td>14%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>3</td>
<td>12%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>1</td>
<td>2%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>1</td>
<td>2%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37/40)</td>
<td>1</td>
<td>5%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>1</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2</td>
<td>4%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Birth injury</td>
<td>2</td>
<td>9%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>2</td>
<td>8%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>1</td>
<td>2%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>1</td>
<td>2%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>3</td>
<td>2%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>3</td>
<td>12%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>0</td>
<td>0%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
<td>0</td>
<td>0%</td>
<td>0.00, 0.88</td>
<td>0.02</td>
</tr>
</tbody>
</table>
## Neonatal Hypoglycaemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Completers</th>
<th>ITT Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN/ICU admission</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Total Event Rate</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Composite Outcome</td>
<td>51</td>
<td>42</td>
</tr>
</tbody>
</table>

### Exclusions
- **a** Exclusions for primary Caesarean section include co-existing gestational diabetes, gestational HTN/PET, LGA, IUGR, pre-term delivery, congenital anomaly that resulted in delivery via Caesarean section.
- **b** Exclusions for neonatal hypoglycaemia include coexisting IUGR, LGA, offspring of mother with gestational diabetes.
- **c** Exclusions for neonatal jaundice include birth injury.
- **d** Exclusions for special care nursery/neonatal intensive care unit admission include admission for LGA, IUGR, pre-term delivery, birth injury, congenital anomaly, neonatal hypoglycaemia, neonatal jaundice.

*Denotes a maternal outcome and n=44 has been used for the analysis.

^Denotes a neonatal outcome and n=46 has been used for the analysis.

# Denotes p-value calculated by negative binomial analysis.

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Allocation

Assessed for eligibility (n=216)

Excluded (n=52)
- Not meeting inclusion criteria (n=41)
- Declined to participate (n=11)
- Other reasons (n=0)

Randomized (n=164)

Allocated to SDI intervention SDI (n=79)
- Completer of intervention (n=53)
- Non-completer of intervention (n=26)
  - Did not tolerate intervention (n=25)
  - Pregnant during intervention (n=1)

Allocated to VLED intervention SDI (n=85)
- Completer of intervention (n=71)
- Non-completer of intervention (n=14)
  - Did not tolerate intervention (n=10)
  - Pregnant during intervention (n=4)

Analyses

Completer only analysis (subjects who completed the 12-week weight loss intervention) (n=22)
- Completer with singleton live births (n=22)

Intention to treat analysis (all subjects regardless of whether they completed the intervention) (n=25)
- Completer with singleton live births (n=22)
- Completer with multifetal gestation (n=0)
- Non-completer with pregnancy during intervention resulting in live birth (n=1)
- Non-completer with pregnancy resulting in a live birth (n=2)

Analysis of live births

Intention to treat analysis (all subjects regardless of whether they completed the intervention (n=44 mothers; 46 neonates)
- Completers with singleton live birth (n=35)
- Completers with multifetal live birth (n=2)
- Non-completer with pregnancy during intervention resulting in live birth (n=4)
- Non-completer with pregnancy resulting in live birth (n=3)
Figure 2a

Weight change from baseline (kg)

Week

ns not significant; * p < 0.05; ** p < 0.01; *** p < 0.001

Figure 2b

Weight change from baseline (kg)

Week

ns not significant; * p < 0.05; ** p < 0.01; *** p < 0.001
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Author/s:
Price, SAL; Sumithran, P; Nankervis, AJ; Permezel, M; Prendergast, LA; Proietto, J

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Date:
2021-09-01

Citation:

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