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Hyperinsulinaemia in pregnancy and gestational outcomes: A case series

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Background: Pathological insulin resistance in pregnancy is associated with an increased risk for complications such as gestational diabetes mellitus and pre-eclampsia. Individuals with pathological insulin resistance also exhibit hyperinsulinaemia. Currently, there are no diagnostic criteria for pathological hyperinsulinaemia in pregnancy that may be used to indicate risk of adverse outcomes.

Aim: This case series aimed to explore the relationship between first trimester insulin response patterns and gestational outcomes.

Setting: Auckland, New Zealand.

Methods: Participants included four pregnant women with prepregnancy body mass index ≥ 25 kg/m^2 and aged 25–35 years. Glucose and insulin response patterns were examined following a 120 min oral glucose tolerance test (OGTT) at 12–15 weeks of gestation using a modified Kraft methodology. Outcomes assessed at 25 and 35 weeks of gestation included gestational weight gain (GWG), blood pressure, fasting capillary blood glucose and foetal growth. Lifestyle and medical information were collected at each trimester. After delivery, total GWG, infant size, delivery method and clinical outcomes were recorded.

Results: Kraft pattern IIB hyperinsulinaemia was identified in two cases. Amongst them, Case #1 experienced excessive GWG, induction of labour and surgically assisted delivery. Case #4 delivered by emergency caesarean, and the neonate required intensive care admission for 17 h. No cases developed hyperglycaemia or hypertension. Infant weights were between 3.75 kg and 3.86 kg.

Conclusion: Dynamic insulin assay provides a promising template to assess metabolic risk in the first trimester of pregnancy. Diagnosing hyperinsulinaemia early in pregnancy means that lifestyle-based initiatives could be introduced earlier to mitigate excess GWG and potential adverse outcomes.

Keywords: hyperinsulinaemia; hyperinsulinemia; hyperinsulinism; gestational diabetes mellitus; gestational weight gain.

Introduction

The global obesity and type 2 diabetes epidemic have risen in parallel with pathological insulin resistance syndromes in pregnancy that have widespread implications for maternal and infant health.[1,2,3,4] In New Zealand (NZ), 27% – 32% of women of child-bearing age are obese.[5] Women who conceive with insulin-resistant obesity will enter pregnancy already at risk of complications, such as gestational diabetes mellitus (GDM), pre-eclampsia and foetal overgrowth.[6]

Changes to maternal insulin metabolism are a normal and essential part of human pregnancy. From the late first trimester, placental hormones including human placental growth hormone and maternal adipokines drive the increase in maternal insulin resistance.[7,8] Concurrently, human placental lactogen stimulates the compensatory expansion of maternal pancreatic beta-cells to enhance insulin secretion and maintain glucose homeostasis.[7] The resulting progressive physiological hyperinsulinaemia and insulin resistance of pregnancy ensure nutrient and energy availability for a growing foetus. However, in women with pre-existing insulin resistance, these physiological gestational changes become augmented by additional maternal metabolic dysfunction, leading to pathological hyperinsulinaemia and insulin resistance.[6,9,10]

Pathological insulin resistance in pregnancy is linked to a milieu of metabolic derangements, including low-grade chronic inflammation, oxidative stress[11] and altered nutrient transport.[12] Infants

Note: Additional supporting information may be found in the online version of this article as Online Appendix 1

born to mothers with either GDM[13,14] and/or obesity[6,15] experience an increased risk of foetal growth restriction (infants born small-for-gestational-age) or overgrowth (macrosomia or infants born large-for-gestational-age [LGA]). There is also an increased risk of delivery complications, including induction of labour, shoulder dystocia, emergency caesarean delivery and neonatal metabolic complications, including hypoglycaemia and respiratory distress. Metabolic dysfunction *in utero* also increases the offspring's risk of developing childhood obesity, type 2 diabetes in early adulthood and/or metabolic syndrome later in life.[16,17,18,19,20]

Pathological hyperinsulinaemia is both a cause and consequence of insulin resistance.[21] Research shows that hyperinsulinaemia plays an important underlying role in the pathogenesis of cardiometabolic and other chronic metabolic diseases.[22] In nonpregnant, glucose-tolerant adults, hyperinsulinaemia could predict the development of type 2 diabetes as early as 20 years in advance.[23] One method used to diagnose hyperinsulinaemia is plotting a curve based on insulin release in response to an oral glucose tolerance test (OGTT).[24,25,26,27] A dysfunctional insulin secretion pattern is characterised by a delayed insulin peak, with or without elevated fasting insulin. Other widely used measures such as the homeostasis model assessment (HOMA) system, based on fasting insulin and glucose, are considered inappropriate for diagnosing hyperinsulinaemia due to the oscillatory nature of insulin release.[24,25]

Pathological hyperinsulinaemia can also be observed during pregnancy. Zhang et al.[28] conducted a large prospective study that included a 180 min OGTT with insulin assay alongside routine screening for GDM at 24–28 weeks of gestation. Amongst the 1695 women diagnosed as having GDM, 62% had a 'dysfunctional' insulin pattern, which was defined as a delayed peak at 2 h or 3 h post glucose load. Regardless of GDM status, this 'dysfunctional' insulin pattern was significantly associated with a higher risk of adverse maternal and neonatal outcomes, including pre-eclampsia, LGA infants and neonatal hypoglycaemia. Similarly, our previous analysis of a pregnant cohort showed that a delayed peak hyperinsulinaemia pattern was characterised among 75% of women with GDM and 31% of those with normal glucose tolerance.[29]

Given that hyperinsulinaemia is part of the aetiology of various chronic noncommunicable metabolic diseases,[22] pilot studies have endeavoured to describe an association between hyperinsulinemia in early gestation (~16 weeks and earlier), the risk of GDM development[30,31,32] and hypertensive disorders in pregnancy.[33,34,35,36] Although these first trimester measures have variable sensitivity and specificity for GDM,[30,32] there is an argument that dynamic insulin measurement could be used as a predictor of other adverse gestational outcomes, independent of GDM status. That is to say, the associations between mid-gestation hyperinsulinaemia and the adverse outcomes described by Zhang et al.[28] could also exist for first trimester insulin assays. The ability to identify women in their first trimester with a metabolic phenotype associated with an increased risk for adverse outcomes could mean that lifestyle-based strategies[37,38] are introduced sooner. A key challenge to investigate this hypothesis further is that, aside from those outlined in the existing research, there are currently no diagnostic algorithms for hyperinsulinaemia specific to pregnancy.

This pilot study aimed to explore the relationship between a woman's first trimester insulin response pattern and gestational outcomes, including glycaemia, gestational weight gain (GWG), foetal growth and obstetric outcomes. A modified version of the Kraft algorithm[27] was applied to diagnose hyperinsulinaemia in a clinical setting that is common practice when screening pregnant women for GDM. It was hypothesised that diagnosing hyperinsulinaemia in the first trimester of pregnancy could be used to identify a woman's risk of adverse pregnancy-related outcomes, thereby providing an earlier opportunity to introduce dietary and lifestyle measures. This study presents a case series of four NZ women identified to have at least one risk factor of GDM who underwent an OGTT with insulin assays in the first trimester of pregnancy.

Methods

We conducted a prospective observational pilot study with four women living in Auckland, NZ. Participants were women at less than 14 weeks of gestation with a naturally conceived singleton pregnancy. Selection criteria included those with a prepregnancy BMI ≥ 25 kg/m^2 and aged between 25 and 35 years. Women were invited to participate by convenience sampling, which included advertising on social media in targeted private Facebook groups (e.g. 'NZ Mums'). Eligible participants confirmed their involvement in the study by providing written informed consent.

Participants were invited to attend an OGTT in the first trimester of pregnancy (< 14 weeks of gestation) at their nearest community pathology clinic (Labtests NZ). Venous blood samples were taken at fasting, then 30 min, 60 min and 120 min following a 75 g glucose drink (Carbotest™). Samples were measured for insulin using chemiluminescence technique, and glucose was measured by ultraviolet method (Roche Cobas) by the commercial pathology service (Labtests NZ). Plasma glucose results were examined according to the NZ Ministry of Health diagnostic criteria where either a fasting plasma glucose $\geq$ 5.5 mmol/L or 120 min plasma glucose $\geq$ 9.0 mmol/L is diagnostic for GDM.[39] Insulin patterns were classified according to Kraft pattern methodology.[27] However, because the Kraft pattern criteria rely on a 180 min insulin assay, the criteria were modified to apply to a 120 min OGTT. This meant replacing the 120 min and 180 min sum value from Kraft patterns I, IIA and IIB with 120 min cut-offs (Table 1). To establish the 120 min insulin cut-off criteria for this current study, new criteria were modelled on the same Kraft dataset previously used by Crofts et al.[27] to determine the percentage of individuals who would be misdiagnosed using only 0–120 min insulin values to ascertain Kraft patterns. Estimated frequencies of misdiagnosed individuals after modelling the modified criteria are provided in Online Appendix 1. Cut-off values for the 120 min criteria were chosen to minimise the proportion

TABLE 1: Modified Kraft pattern criteria to diagnose hyperinsulinaemia from a 120 min oral glucose tolerance test.

Kraft pattern	Description
Pattern I, modified (normal insulin)	Fasting insulin ≤ 30 μU/mL
	30 min or 60 min peak
	120 min ≤ 36 μU/mL
Pattern IIA, modified (borderline)	Fasting insulin ≤ 50 μU/mL
	30 min or 60 min peak
	120 min > 36, < 65
	or
	Fasting insulin 31 μU/mL – 50 μU/mL
	30 min or 60 min peak
	120 min ≤ 36 μU/mL
Pattern IIB, modified (hyperinsulinaemia)	Fasting insulin ≤ 50 μU/mL
	30 min or 60 min peak
	120 min ≥ 65 μU/mL
Pattern III (hyperinsulinaemia)	Fasting insulin ≤ 50 μU/mL
	Delayed peak (120 min or not observed)
Pattern IV (hyperinsulinaemia)	Fasting insulin > 50 μU/mL
Pattern V (hypoinsulinaemia)	All values < 30 μU/mL

Source: Adapted from Crofts C, Schofield G, Zinn C, Wheldon M, Kraft J. Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database. *Diabetes Res Clin Pract*. 2016;118:50–57. https://doi.org/10.1016/j.diabres.2016.06.007

of individuals underdiagnosed (i.e. being misdiagnosed as being *healthier* than they are), whilst allowing for a higher percentage of individuals who could be misdiagnosed as having more advanced hyperinsulinaemia. These more cautious criteria were chosen versus more lenient criteria because initial management strategies for hyperinsulinaemia are based around reinforcing healthy lifestyle practices such as healthy eating and physical activity.

Further health, dietary and lifestyle information was collected in face-to-face interviews at the time of each OGTT. This information included gestational age, self-reported prepregnancy weight and height, recent medical history including any prescription medications and supplements and lead maternity carer details. A dietary and lifestyle assessment included a 24 h food recall, a 20-item food frequency questionnaire and qualitative questions describing the woman's diet pattern, recent dietary changes, exercise pattern and recent changes to physical activity. This questionnaire was repeated at 25 and 35 weeks of gestation by a remote video or phone interview. Participants collected their own capillary fasting blood glucose levels for seven days at 25 and 35 weeks of gestation (FreeStyle Optium Neo meter and glucose test strips). The date, time and glucose reading result were recorded and e-mailed to the researcher on a log sheet.

Participants were provided with an additional written questionnaire to complete with their lead maternity carer as part of standard antenatal assessments. They were also asked to provide a record of metabolic parameters (first trimester glycated haemoglobin [HbA1c], blood pressure, recommended total GWG and current weight), foetal growth ultrasonography measures (timing and frequency according to lead maternity carer guidance) and medical concerns (e.g. thyroid problem, weight gain, iron deficiency or foetal abnormalities). This questionnaire was repeated at 25 and 35 weeks of gestation and returned by e-mail.

Women received standard antenatal care from their community lead maternity carer. Maternal and foetal obstetric outcome information was collected during a postnatal telephone interview with the women. Information collected included gestational age at birth, delivery method, medical interventions used and neonatal birth weight, length and respective percentiles according to the INTERGROWTH-21st project neonatal growth charts.[40]

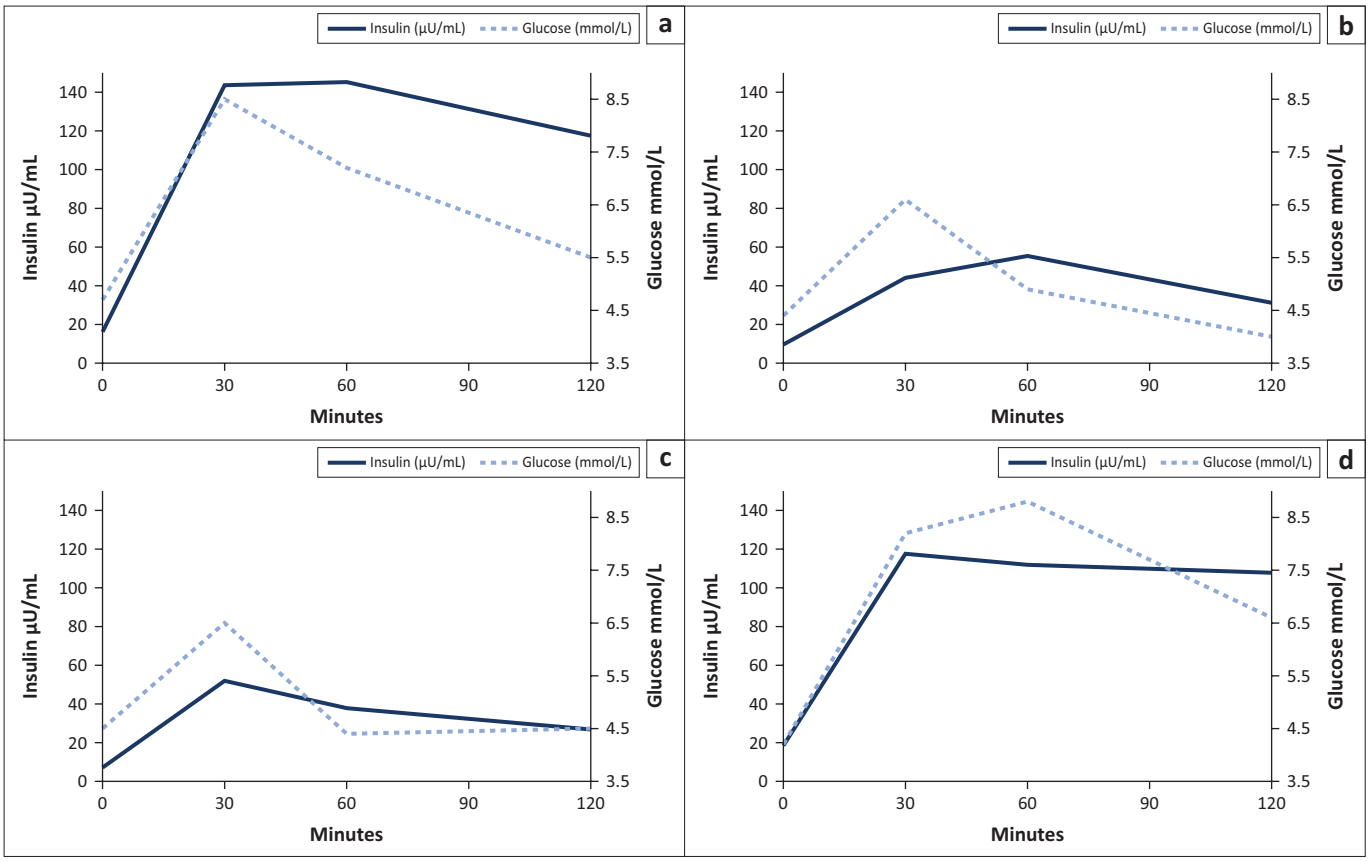
Case presentation

Insulin and glucose assays performed following a 120 min OGTT measured between 12 + 1 (weeks plus days) and 14+5 weeks of gestation for each case study are presented in Figure 1. All women had normal fasting insulin levels ≤ 30 μU/mL, as compared to the criteria in Table 1. Insulin responses from all four women had an insulin peak at either 30 min or 60 min following the 75 g glucose bolus, which is suggestive of a normal first-phase insulin secretory response. Cases #1 and #4 had an elevated 120 min insulin value (Case #1: 117.5 μU/mL; Case #4: 107.8 μU/mL), which is characteristic of Kraft pattern IIB hyperinsulinaemia. Cases #2 and #3 presented with normal insulin tolerance. For Case #2, the insulin response peaked at 60 min (55.4 μU/mL), whilst for Case #3 a peak insulin of 51.9 μU/mL was established at 30 min. All women had normal glucose tolerances according to the NZ Ministry of Health diagnostic criteria for GDM.[39]

Baseline characteristics from the four case studies are presented in Table 2. Information on medications, nutritional supplements and dietary information collected at each trimester are included in Online Appendix 1.

Case #1: Kraft pattern IIB (hyperinsulinaemia)

Case #1 was a 30-year-old primigravida Caucasian woman with no pre-existing medical conditions. Self-reported body weight before conception was 82.0 kg (BMI 28.4 kg/m^2). She had conceived naturally after ceasing contraception (medroxyprogesterone acetate [Depo Provera™] injection) 24 months prior and had a normal HbA1c of 33 mmol/mol. Metabolic parameters collected at 25 and 35 weeks of gestation are shown in Table 3. Total GWG was 19.0 kg, 7.5 kg – 12.0 kg in excess of NZ Ministry of Health and Institute of Medicine (IOM) guidelines for women with a BMI between 25.0 kg/m^2 and 29.5 kg/m^2.[39,41] Lead maternity care antenatal clinical notes indicated foetal growth above the 90th percentile, which resulted in additional growth scans during the third trimester (Table 4). Foetal ultrasonography measured taken at 27 + 2, 32 + 3 and 36 + 3 but not 34 + 2 weeks indicated foetal biparietal diameter above the 95th percentile and between the 50th and 95th percentile for head and abdominal circumference and femur length.[42] Dietary information from 24 h food recall and FFQs collected at each trimester indicated no remarkable dietary changes (Online Appendix 1). Self-reported physical activity included walking, which was reduced in the third trimester.



OGTT, oral glucose tolerance test.

FIGURE 1: Glucose and insulin response patterns following 75 g oral glucose tolerance test. (a) Case #1: Normal glucose tolerance, Kraft IIB hyperinsulinaemia – 75 g OGTT glucose and insulin assay performed 12 + 1 weeks' gestation. (b) Case #2: Normal glucose tolerance, Kraft I normal – 75 g OGTT glucose and insulin assay performed 14 + 5 weeks' gestation. (c) Case #3: Normal glucose tolerance, Kraft I normal – 75 g OGTT glucose and insulin assay performed 11+6 weeks' gestation. (d) Case #4: Normal glucose tolerance, Kraft IIB hyperinsulinaemia – 75 g OGTT glucose and insulin assay performed 14+5 weeks' gestation.

TABLE 2: Baseline characteristics.

Participant characteristics	Case study 1	Case study 2	Case study 3	Case study 4
Age (years)	30	30	30	28
Parity	0	1	0	0
Prepregnancy weight (kg)	82.0	75.0	80.0	92.0
Prepregnancy BMI (kg/m^2)	28.4	26.6	25.5	37.8
HbA1c 1st tri (mmol/mol)	33	31	33	35

BMI, body mass index; HbA1c, glycated haemoglobin.

TABLE 3: Metabolic parameters collected throughout gestation.

Participant characteristics	Case study 1	Case study 2	Case study 3	Case study 4
Weight 25 wk (kg)	91.6	68.5	85.4	91.0
Weight 35 wk (kg)	98.0	80.0	91.7	94.8
Weight 38 wk (kg)	101.0	84.0	92.5	96.0
Total GWG (kg)	19.0	9.0	12.5	4.0
Blood pressure 1st tri (systolic/diastolic mmHg)	122/80	110/60	110/60	100/65
Blood pressure 2nd tri (systolic/diastolic mmHg)	118/70	104/63	110/66	92/62
Blood pressure 3rd tri (systolic/diastolic mmHg)	120/75	90/60	120/70	102/72
SMBGL 25 wk (mmol/L)				
Mean	3.9	4.4	4.2	4.4
Range	3.5–4.1	4.2–4.8	4.1–4.4	3.7–4.8
SMBGL 35 wk (mmol/L)				
Mean	4.0	4.3	4.0	4.2
Range	3.8–4.1	4.1–4.8	3.8–4.2	3.8–4.4

GWG, gestational weight gain; SMBGL, self-measured fasting capillary blood glucose, 7-day average; wk, weeks; Tri, trimester.

Labour was induced by misoprostol at 39 + 5 weeks of gestation. She received epidural anaesthesia and oxytocin. Delivery was assisted by ventouse and forceps, requiring episiotomy. Complications included meconium present in amniotic fluid, foetal shoulder dystocia and a 3rd degree perineal tear. The neonate was born weighing 3.80 kg (50th – 90th percentile) and length 51 cm (50th – 90th percentile).[40]

Case #2: Kraft pattern I (normal insulin tolerance)

Case #2 was a 30-year-old secundigravida Caucasian woman. Self-reported prepregnancy weight was 75 kg and BMI 26.6 kg/m^2. First trimester antenatal assessments confirm normal HbA1c of 31 mmol/mol and blood pressure of 110/60 mmHg, which remained stable during the second trimester. Self-measured capillary fasting glucose levels were within normal ranges at 25 weeks (4.2 mmol/L – 4.8 mmol/L) and 35 weeks of gestation (4.1 mmol/L – 4.8 mmol/L) (Table 2). Case #2 did not undergo further screening or diagnostic tests for GDM at 24 weeks of gestation. Total GWG throughout pregnancy was 9.0 kg, within the recommended 7.0 kg – 11.5 kg.[39,41]

According to lead maternity care records from 35 weeks of gestation, Case #2 presented with low blood pressure (90/60 mmHg) and irregular uterine contractions, noted by the lead maternity carer as an 'irritable uterus', as a threat for

TABLE 4: Foetal and birth outcomes.

Foetal and neonatal characteristics	Case 1	Percentile	Case 2	Percentile	Case 3	Percentile	Case 4	Percentile
Foetal growth (2nd tri)								
Gestational age (wk + day)	27 + 2	-	No growth scan, anatomy scan normal	-	No growth scan, anatomy scan normal	-	28 + 5	-
BPD†	77	> 95th		-		-	74	50th – 95th
HC†	265	50th – 95th		-		-	279	50th – 95th
AC†	251	50th – 95th		-		-	262	50th – 95th
FL†	53	50th – 95th		-		-	56	50th – 95th
EFW (g)	1296	-		-		-	1488	
Foetal growth (3rd tri)								
Gestational age (wk + day)	36 + 3§	-	No growth scan	-	34 + 6	-	37 + 4	-
BPD (mm)†	97	> 95th		-	94	> 95th	92	5th – 50th
HC (mm)†	336	50th – 95th		-	333	50th – 95th	324	5th – 50th
AC (mm)†	351	50th – 95th		-	320 (50th – 95th)	50th – 95th	352	50th – 95th
FL (mm)†	71	50th – 95th		-	67 (50th – 95th)	50th – 95th	70	5th – 50th
EFW (g)	3406	-		-	2817	-	3340	-
Delivery								
Gestational age (wk + day)	39 + 5	-	39 + 1	-	39 + 4	-	40 + 5	-
Gender	Male	-	Male	-	Male	-	Male	-
Birth weight (kg)‡	3.80	50th – 90th	3.86	90th – 97th	3.76	50th – 90th	3.75	50th – 90th
Birth length (cm)‡	51	50th – 90th	50	50th – 90th	51.5 (50th – 90th)	50th – 90th	55	> 97th

BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; Wk, weeks. Tri, trimester.
†, National Women's Health.[42]; ‡, Villar et al.[40]; §, Additional growth scans from Case #1 at 32 + 3 and 34 + 2 weeks' gestation not shown.

preterm labour. Self-reported physical activity reduced in the third trimester due to pain, discomfort and heat exhaustion reduced during this time. Total energy from self-reported dietary intake from 24 h food recall at each time point was remarkably lower than expected requirements (~38% – 43% of 9800 kJ/day vs recorded 3741 kJ/day – 4231 kJ/day).[43] At each of these time points, Case #2 reported that her intake was lower than usual and that she experienced nausea in trimester 1, acute gastroenteritis from foodborne illness in trimester 2 and lethargy related to iron deficiency in trimester 2 and 3. Reduced intake during trimester 1 is also consistent with 6.5 kg weight loss observed between prepregnancy and weight at 25 weeks of gestation.

Case #2 delivered a male neonate at 39 + 1 weeks of gestation. The labour and birth were unassisted without complications to the neonate. The neonate was born weighing 3.86 kg (90th – 97th percentile) and length 50 cm (50th – 90th percentile).[40] Partial placental attachment and maternal haemorrhage shortly after the birth indicated admission to Middlemore Hospital, requiring surgical intervention.

Case #3: Kraft pattern I (normal insulin tolerance)

Case #3 was a 30-year-old primigravida Caucasian woman with no pre-existing medical conditions. Although medically primigravida, she suspected miscarrying a conceptus at 4–5 weeks of gestation, 2 months prior to the confirmed pregnancy. Prepregnancy weight was 80.0 kg and BMI 25.5 kg/m^2. First trimester antenatal assessments confirm a normal HbA1c of 33 mmol/mol and blood pressure of 110/60 mmHg, which remained stable throughout gestation. First trimester antenatal biochemistry also revealed mild thrombocytopenia, which continued into the second trimester. Self-measured capillary glucose levels were nonremarkable at 25 weeks (4.1 mmol/L – 4.4 mmol/L) and 35 weeks of gestation (3.8 mmol/L – 4.2 mmol/L) (Table 3). Total GWG was 12.5 kg, 1.0 kg excess of the recommended 7.0 kg – 11.5 kg.[39,41] Case #3 did not undergo further screening or diagnostic tests for GDM at 24 weeks of gestation. Dietary information collected at each trimester indicated no remarkable dietary changes (Online Appendix 1). Physical activity in the first trimester included weight training and running, which was replaced by walking and yoga in the second and third trimesters.

Foetal growth ultrasound performed on 34 + 6 weeks of gestation reported foetal biparietal diameter above the 95th percentile and head and abdominal circumference and femur length within the 50th – 95th percentile.[42] Case #3 gave birth to a male neonate at 39 + 4 weeks following a natural labour. Birth weight was 3.76 kg (50th – 90th percentile) and length 51 cm (50th – 90th percentile).[40] No maternal or neonatal complications were reported.

Case #4: Kraft pattern IIB (hyperinsulinaemia)

Case #4 was a 28-year-old primigravida Caucasian woman. Her self-reported prepregnancy weight was 92.0 kg (BMI 37.8 kg/m^2) and antenatal biochemistry confirmed a normal HbA1c of 35.0 mmol/mol (Table 3). Self-measured capillary glucose levels at 25 weeks ranged from 3.7 mmol/L to 4.8 mmol/L and 3.8 mmol/L – 4.4 mmol/L 35 weeks (Table 3). A secondary OGTT performed at 27 + 5 weeks of gestation confirmed normal glucose tolerance (fasting venous glucose 4.0 mmol/L; 2 h post 75 g OGTT 7.4 mmol/L).

Case #4 was advised by her lead maternity carer in trimester 1 to avoid excessive GWG due to the risks associated with obesity in pregnancy. She reported changing her dietary habits at the beginning of pregnancy to 'eat healthier', which included an increased daily intake of vegetables, fruits and

protein-rich foods (meat, eggs and dairy) and reduced intake of sugar and ultra-processed snack foods. As a result, Case #4 gained a total of 4 kg during pregnancy after an initial 2 kg weight loss in the first trimester (Table 3). Foetal growth ultrasonography from 28 + 5 weeks suggested normal growth patterns between the 50th and 95th percentiles for all measures. At 37 + 4 weeks of gestation, biparietal diameter, head circumference and femur length were recorded in the 5th – 50th percentile (Table 4).[42]

Dietary information from FFQs collected at each trimester indicated an increase in processed meat and sugar-free drink consumption and decreased consumption of refined grains, nuts and spreads. Dietary recall analysis from 24 h showed no remarkable change in food intake between the three trimesters (Online Appendix 1). Self-reported physical activity included daily walking, which was replaced for swimming in the second trimester.

Labour commenced naturally at 40 weeks of gestation and remained in the latent stage for five days. The posteriorly positioned foetus was delivered by an emergency caesarean section with epidural anaesthesia. The male neonate weighing 3.75 kg (50th – 90th percentile) and length 55 cm (> 97th percentile)[40] was compromised on delivery (heart rate of 55 beats per minutes [pbm]) and admitted to neonatal intensive care for 17 h for oxygen, intravenous glucose and enteral feeding.

Discussion

We presented four clinically healthy pregnant women with BMIs > 25 kg/m^2 who had varying obstetric outcomes. Dynamic insulin tolerance examined from 12 to 15 weeks of gestation varied between the participants. Presented cases included two women with Kraft IIB hyperinsulinaemia and two women with normal insulin tolerance (Kraft I).

Observations from this case series can be compared against previous literature that has, to a limited degree, drawn associations between varying descriptions of hyperinsulinaemia and adverse pregnancy outcomes. In a recent prospective observational study that included 2432 pregnant women, Zhang et al.[28] defined a 'dysfunctional' insulin pattern as one that has a delayed 120 min or 180 min peak insulin response following an OGTT, which is similar to Kraft pattern III (hyperinsulinaemia) used in this case series. Logistic regression analysis showed that Zhang's Type II delayed-peak insulin secretion pattern was significantly associated with a higher risk for pre-eclampsia, LGA and neonatal hypoglycaemia, in both normal glucose-tolerant and GDM women. Furthermore, three large cohort studies have characterised metabolic phenotypes amongst women with established GDM based on insulin secretory responses and insulin resistance.[44,45,46] Although using varied methodologies, these studies showed that women grouped as being 'insulin resistant-GDM', with or without first-phase beta-cell dysfunction, have exaggerated postprandial insulin responses and experience the greatest risk for adverse pregnancy outcomes compared to GDM women with greater insulin sensitivity. Gestational diabetes mellitus women grouped as having an 'insulin secretion defect', without insulin resistance, had lower postprandial insulin responses and similar outcomes as their non-GDM pregnant counterparts. Outside of pregnancy, Hayashi et al.[26] demonstrated a temporal relationship between 'delayed peak' hyperinsulinaemia, which is similar to Kraft pattern III and Zhang's Type II delayed-peak pattern, and the development of type 2 diabetes over a 5–11-year period. None of the cases presented in this case series developed GDM, pre-eclampsia or delivered LGA infants. However, it is noteworthy that Cases #1 and #4 both experienced difficulties in labour requiring delivery assistance (Case #1) and emergency caesarean (Case #4).

Case #1 experienced excess GWG throughout pregnancy and in the second and third trimesters, foetal biparietal diameter measured above the 95th percentile. Due to the presumed risks associated with excess GWG and foetal overgrowth, Case #1 received a medical induction at 39 + 5 weeks of gestation, which was complicated by shoulder dystocia and meconium aspiration, requiring surgical assistance (ventouse, forceps and episiotomy). These delivery complications, however, did not appear to be directly a result of foetal overgrowth, because the infant born to Case #1 was of normal weight and length for gestational age (between the 50th and 95th percentiles).[40] According to the recently revised clinical practice guidelines for the induction of labour in NZ, it is suggested that maternal obesity or suspected foetal macrosomia without other risk factors (i.e. non-GDM women) does not indicate induction of labour due to insufficient evidence for any proposed benefit.[47] Furthermore, Chandrasekaran[48] argues that third trimester ultrasound lacks the required precision to diagnose LGA infants and recommends shared decision-making to outweigh perceived risks and benefits of interventions. Although infant birthweight from Case #1 was in the upper range of the 50th – 90th percentile, it is likely that neonatal shoulder dystocia was unrelated to maternal insulin resistance. Instead, difficulties during labour may have occurred as a result of the medical interventions Case #1 received during her induction of labour. Ironically, a potentially unnecessary induction may have been recommended for Case #1 due to the *perceived* risks from excessive GWG. That is to say, hyperinsulinaemia at the beginning of pregnancy predisposed Case #1 to excess GWG, ultimately leading down a path to maternal and neonatal birth trauma via medical intervention.

Shoulder dystocia is one of many established birthing complications that occur more frequently in women with excess GWG, BMI ≥ 25 kg/m^2,[15] and/or hyperglycaemia in pregnancy.[14] It often results from foetal macrosomia.[49] The Pedersen[50] hypothesis describes that excess foetal growth is driven by the passive oversupply of maternal glucose (hyperglycaemia), resulting in foetal hyperglycaemia and hyperinsulinaemia. Thus, Pedersen implied maternal glucose levels were the primary driver of foetal overgrowth via the

foetal insulin response. However, the historical hypothesis does not explain how infants born LGA can occur at near equivocal rates in non-GDM mothers with obesity (odds ratio [OR]: 1.7) as those with GDM (OR: 2.2),[14] thus suggesting an alternate mechanism at play. Case study #1 presented with Kraft pattern IIB hyperinsulinaemia in the first trimester. Furthermore, excess GWG could have amplified insulin resistance and hyperinsulinaemia as gestation progressed, increasing the risk of foetal overgrowth.[51] These changes occurred independently of glucose status because both the OGTT at 26 weeks of gestation and fasting capillary glucose levels confirmed normoglycaemia. There are several mechanisms that could explain the relationship between maternal hyperinsulinaemia and foetal overgrowth. Insulin-binding placental insulin receptors have the potential to activate insulin/insulin-like-growth-factor 1 (IGF-1) and mammalian target of rapamycin (mTOR) signal transduction pathways to enhance nutrient transport across the placenta.[52,53,54] Sobrevia et al.[12] proposed that hyperinsulinaemia leads to endoplasmic reticulum stress that drives activation of maternal adipokines and dyslipidaemia. Furthermore, Sobrevia et al. discuss that hyperinsulinaemia could be the mechanistic driver in GDM pregnancies that alters placental vasculature and nutrient delivery, leading to increased fatty acid transfer, reduced docosahexaenoic acid and altered composition of high-density lipoprotein particles in fetoplacental circulation. Increased lipid transport as an energy supply to the foetus may explain a higher incidence of foetal overgrowth, particularly in the context of mothers with normal glycaemia. Interestingly, altered placental vasculature function may also be implicated in placental retention,[55] which was observed in Case #2, implying a hypothetical role of hyperinsulinaemia in the pathogenesis of this condition.[56]

Diagnostic and therapeutic targets to define normal glycaemic patterns in pregnancy have received considerable controversy. The landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) trial, which included over 25 000 women worldwide, suggested that maternal glucose levels below the previously accepted diagnostic thresholds for GDM were predictive of LGA and foetal hyperinsulinaemia.[14] In response, the International Association of Diabetes in Pregnancy Study Group and the American Diabetes Association recommended new lower diagnostic criteria for GDM.[57] Furthermore, glycaemic targets for women with GDM have also been a source of controversy. Hernandez et al.[58] performed a systematic review and collated glycaemic patterns from healthy pregnant women in 11 studies between 1975 and 2008. Their results showed remarkably lower glycaemic patterns than targets set for women with GDM, suggesting stricter glycaemic targets are required to reduce the risk of foetal overgrowth amongst women with GDM and obesity in pregnancy. Indeed, the proportion of undetected hyperglycaemia in pregnancy due to lenient criteria is unknown. When compared against the stricter thresholds proposed by Hernandez et al.,[58] Case #1 and Case #4 from this case series, both of whom were characterised as having hyperinsulinaemia in trimester 1, could be described as borderline hyperglycaemic based on fasting (proposed normal: 3.4 mmol/L – 4.4 mmol/L, vs 4.7 mmol/L for Case #1), 1 h (proposed normal: 5.3 mmol/L – 6.8 mmol/L, vs 7.2 mmol/L for Case #1 and 8.8 mmol/L for Case #4) and 120 min glucose levels following the OGTT (proposed normal: 4.9 mmol/L – 6.1 mmol/L, vs 6.6 mmol/L for Case #4). Noting this relationship in Cases #1 and #4, it is possible that these 'normal glycaemic' women may have had excess maternal glucose available throughout pregnancy which, in line with the Pedersen hypothesis,[50] could drive foetal hyperinsulinaemia.

Gestational weight gain is one of the most significant and modifiable factors in pregnancy, affecting maternal and foetal health. Dietary and lifestyle interventions that encourage healthy GWG observe a reduced risk of GDM[37] and other associated adverse outcomes such as caesarean delivery, macrosomia, neonatal respiratory morbidity and maternal hypertension.[59] Excess GWG also has been positively associated with higher neonatal adiposity[60,61,62] and LGA incidence[63] in numerous cohort studies. Varying GWG outcomes for Cases #1 and #4, both of whom had Kraft IIB hyperinsulinaemia in this case series, may explain differences in obstetric outcomes observed. Case #1 (prepregnancy BMI 28.4 kg/m^2) gained 19 kg throughout pregnancy, amounting to an excess of 7.5 kg – 12.0 kg. However, Case #4's (prepregnancy BMI 37.8 kg/m^2) total GWG was below the recommended 5.0 kg – 9.0 kg.[39,41] These GWG differences were reflected in nutrition and physical activity behaviours described by Cases #1 and #4. During the study period, Case #4 noted changes in dietary behaviours toward a 'healthier' eating pattern to circumvent gestational risks associated with obesity in pregnancy. Lower GWG experienced by Case #4 could have mitigated her risk of foetal overgrowth or hyperglycaemia, thus allowing natural labour. Unfortunately, delivery was ultimately complicated by an emergency caesarean due to a prolonged latent phase of labour and posterior foetal position. Comparing outcomes between Cases #1 and #4, it could be argued that had Case #1 been provided with lifestyle-based strategies early in pregnancy to achieve GWG within the Institute of Medicine guidelines,[39,41] induction of labour and birth trauma may have been avoided. Interestingly, these experiences are contrasted against Case #3 whose GWG was within 1 kg of recommendations[39,41] and had a natural labour and delivery without adverse outcomes. It is speculated that Case #3's appropriate GWG and normal insulin tolerance pattern were likely contributing factors to a low risk profile for adverse outcomes.

This is the first study that, to the researchers' knowledge, examines maternal outcomes across the gestational period in relation to a first trimester insulin pattern. A strength of this case series was that personal dietary and lifestyle information were compiled, as well as clinical changes that are known to influence gestational outcomes. Because it is known that the presence of a certain risk factor does not guarantee an adverse

outcome, this case study design allowed contextualised interpretation of individual risk factors and outcomes. A further strength is that a modified Kraft pattern criteria was modelled to make the algorithm applicable to a 120 min OGTT, versus the original criteria that required a 180 min insulin value to diagnose hyperinsulinaemia (Patterns I, IIA and IIB). These criteria are more practical to apply clinically as the majority of OGTTs used in clinical practice involve a 120 min test. This is especially important for pregnant women who may find it difficult to fast for more than 2 h following the glucose bolus, especially after an overnight fast. Further work is needed to validate these criteria, because there are currently no standard diagnostics used to define hyperinsulinaemia in pregnancy. Timing for insulin assessment must also be defined in pregnancy, because insulin secretion and sensitivity progressively change after placental formation near the end of the first trimester, at approximately 10–12 weeks of gestation.[64] Placental-induced hyperinsulinaemia may have been a confounding variable in two women from this case series (Case #2 and Case #4) who underwent OGTT testing at 14 + 5 weeks of gestation due to practical limitations. The key limitation of this case series is that the interpretation of case series data is limited to speculation. As a result, conclusions cannot be drawn nor can any associations be made with certainty from this participant group. It is also acknowledged there are many confounding characteristics of human pregnancy that can increase the risk of adverse outcomes. These include various intrinsic maternal and paternal factors, as well as external antenatal and birth care influences. Due to the individual nature of pregnancy and delivery, even the absence of risk factors does not guarantee that pregnancy comes without vulnerabilities. A further limitation is that the foetal growth assessments used were requested at the discretion of the women's lead maternity carers. Sequential growth measures in trimester 3 were only available for Case #1 and were not plotted on customised growth charts, thereby limiting interpretation. The researchers therefore recommend that this case series be repeated with a broader sample size to further explore the heterogeneity of insulin patterns in early gestation and establish statistical power that may draw associations toward adverse gestational outcomes.

Conclusion

Dynamic insulin assay provides a promising template that could assess a woman's metabolic risk early in gestation. Further studies with larger participant cohorts are needed to characterise the metabolic phenotype of women with hyperinsulinaemia in pregnancy according to different Kraft patterns. Analyses from larger cohorts examining risks for clinical endpoints such as gestational hypertension, pre-eclampsia, hyperglycaemia and LGA infants could also be used to inform future screening tools applicable in a clinical setting. Diagnosing these women early in pregnancy could mean that lifestyle-based initiatives could be introduced sooner to mitigate excess GWG and potential adverse maternal and neonatal outcomes.

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Competing interests

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Authors' contributions

All authors contributed to the formulation of the research question and study design. S.N. conducted data collection, analysis and contributed to manuscript preparation. C.C. and C.Z. contributed to manuscript preparation.

Ethical considerations

Ethical approval for this study was obtained from the Northern Health and Disability Ethical Committee (ref. no. 19/NTA/124/AM01) and Auckland University of Technology Ethics Committee (ref. no. 20/216).

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Data availability

Due to the identifiable nature of the individual cases presented, further data are available on request at author (S.M.N.) discretion.

Disclaimer

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