Endocrinology, Diabetes & Metabolism CASE REPORTS

U Kampmann and others | Extreme insulin resistance during pregnancy

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Extreme insulin resistance during pregnancy: a therapeutic challenge

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Summary

During pregnancy, maternal tissues become increasingly insensitive to insulin in order to liberate nutritional supply to the growing fetus, but occasionally insulin resistance in pregnancy becomes severe and the treatment challenging. We report a rare and clinically difficult case of extreme insulin resistance with daily insulin requirements of 1420 IU/day during pregnancy in an obese 36-year-old woman with type 2 diabetes (T2D) and polycystic ovary syndrome (PCOS). The woman was referred to the outpatient clinic at gestational week 12 + 2 with a hemoglobin A1c (HbA1c) at 59 mmol/mol. Insulin treatment was initiated immediately using Novomix 30, and the doses were progressively increased, peaking at 1420 units/day at week 34 + 4. At week 35 + 0, there was an abrupt fall in insulin requirements, but with no signs of placental insufficiency. At week 36 + 1 a, healthy baby with no hypoglycemia was delivered by cesarean section. Blood samples were taken late in pregnancy to search for causes of extreme insulin resistance and showed high levels of C-peptide, proinsulin, insulin-like growth factor (IGF-1), mannan-binding-lectin (MBL) and leptin. CRP was mildly elevated, but otherwise, levels of inflammatory markers were normal. Insulin antibodies were undetectable, and no mutations in the insulin receptor (INSR) gene were found. The explanation for the severe insulin resistance, in this case, can be ascribed to PCOS, obesity, profound weight gain, hyperleptinemia and inactivity. This is the first case of extreme insulin resistance during pregnancy, with insulin requirements close to 1500 IU/day with a successful outcome, illustrating the importance of a close interdisciplinary collaboration between patient, obstetricians and endocrinologists.

Learning points:

- This is the first case of extreme insulin resistance during pregnancy, with insulin requirements of up to 1420 IU/day with a successful outcome without significant fetal macrosomia and hypoglycemia.
- Obesity, PCOS, T2D and high levels of leptin and IGF-1 are predictors of severe insulin resistance in pregnancy.
- A close collaboration between patient, obstetricians and endocrinologists is crucial for tailoring the best possible treatment for pregnant women with diabetes, beneficial for both the mother and her child.

Background

During pregnancy, maternal tissues become increasingly insensitive to insulin in order to redistribute an adequate amount of nutritional supply to the growing fetus. The degree of maternal insulin resistance during pregnancy is associated with the degree of glucose flux from the mother to the fetus (1). Maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia, which causes fetal macrosomia – one of the most common and serious pregnancy complications of maternal diabetes and obesity (2). A 50–70% decrease in insulin sensitivity is seen with advancing gestation in women with normal glucose tolerance and with diabetes (1). Occasionally, insulin resistance in pregnancy becomes severe, and the treatment is a challenge to both doctor and patient.

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Here we describe a rare and clinically challenging case, concerning a pregnant woman with T2D and extreme insulin resistance with insulin requirements of up to 1420 IU insulin per day.

Case presentation

A 36-year-old woman, diagnosed with PCOS and T2D 7 years previously, was referred to the outpatient clinic for pregnant women with diabetes at Aarhus University Hospital (AUH) in pregnancy week 12+2. Prior to pregnancy, she had had irregular periods, but a significant weight loss of 30 kg let to regular periods and a spontaneous pregnancy. The patient's pre-pregnancy BMI was 40 kg/m^2, and her blood pressure was 136/71 mmHg at the first visit and remained stable throughout pregnancy. She had previously been treated with metformin, liraglutide, and an ACE inhibitor, but her general practitioner had discontinued all medication after the weight loss as HbA1c was 41 mmol/mol and blood pressure was normal. In addition, the woman did not have any medical history or any clinical or biochemical features of lipodystrophy, severe acanthosis nigricans, hirsutism, obstructive sleep apnea, Cushing's syndrome, acromegaly or hyperthyroidism that could contribute to severe insulin resistance.

When the patient was referred to the outpatient clinic, HbA1c was 59 mmol/mol. Insulin treatment was initiated immediately using Novomix 30 (insulin aspart with both a rapid-acting and an intermediate-acting effect, in the ratio 30/70) 20 units/day. The doses were progressively increased (Fig. 1A and Table 1) and when the patient reached 180 units/day, the insulin regime was changed to Insulatard (intermediate-acting human insulin isophane) twice a day and Novorapid (insulin aspart with a rapid-acting effect) three to five times a day. When the patient reached 1420 units/day at week 34+4, additional blood samples were taken to search for the cause of this extreme insulin resistance. At week 35+0, there was an abrupt fall in insulin requirements to 720 units/day, but with no signs of placental insufficiency as estimated by fetal heart rate tracings and fetal ultrasound scans, including flow measurements. The patient was admitted for observation, and insulin requirements and blood glucose continued to fall. At week 35+4, the patient had no insulin requirements and kept a stable blood glucose at around 6 mmol/L for the next 4 days until delivery by cesarean section at week 36+1, after an unsuccessful attempt of induction of labor due to the dramatic change in insulin requirements.

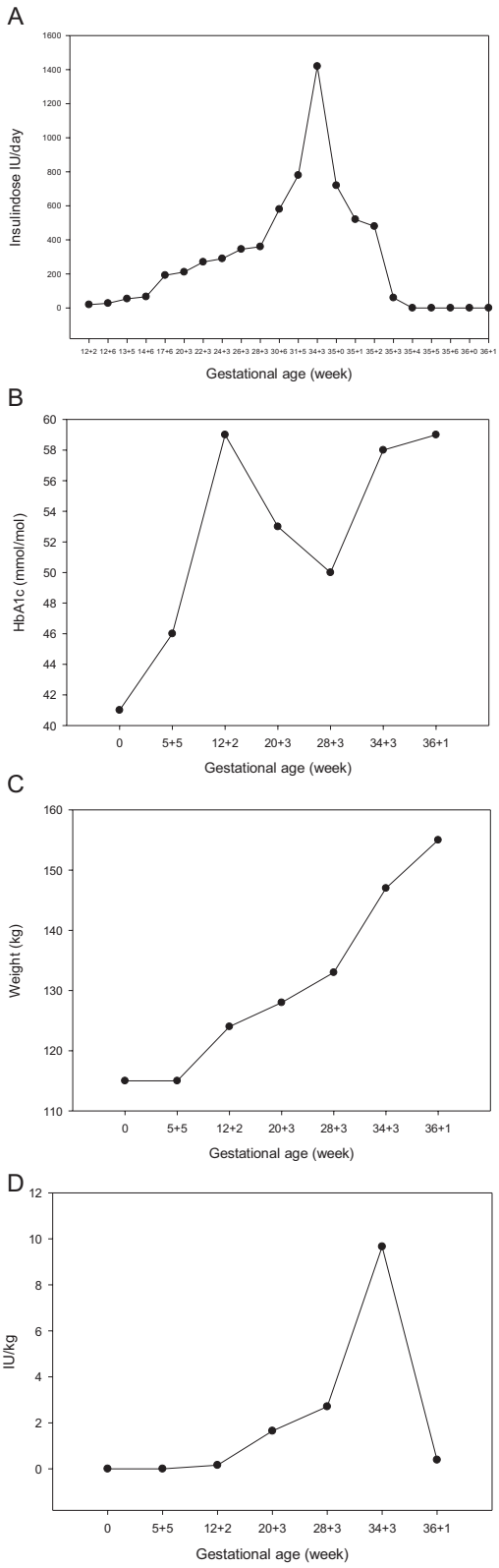

Figure 1
Changes in insulin doses (A) and HbA1c (B) and weight (C) and (D) insulin units/kg during pregnancy.

Table 1 Insulin doses during pregnancy.

Gestational age (week)	**Weight** (kg)	**Hba1C** (mmol/mol)	**Insulin dose** (IU)	**Total daily dose** (IU/day)	**Insulin dose/weight** (IU/kg)
12 + 2		59	Novomix 30 10 IU x 2	20	0.16
12 + 6			Novomix 30 14 IU x 2	28	
13 + 5			Novomix 30 18 IU x 3	54	
14 + 6			Novomix 30 24+18+24 IU	66	
17 + 6			Novomix 30 66 + 30 + 66 + Insulatard 30 IU	192	
20 + 3		53	90 + 0 + 35 IU Insulatard (Ins) 26 + 20 + 40 IU Novorapid (NR)	211	1.65
22 + 3			90 + 0 + 40 IU Ins 40 + 50 + 60 IU NR	270	
24 + 3			100 + 0 + 40 IU Ins 40 + 50 + 60 IU NR	290	
26 + 3			120 + 0 + 50 IU Ins 60 + 50 + 65 IU NR	345	
28 + 3		50	130 + 0 + 60 IU Ins 40 + 50 + 80 IU NR	360	2.71
30 + 6			150 + 0 + 90 IU Ins 120 + 100 + 120 IU NR	580	
31 + 5			120 + 120 + 120 IU Ins 120 + 120 + 120 + 60 IU NR	780	
34 + 3		58	180 + 0 + 120 IU Ins 180 + 180 + 300 + 60 IU NR + 200 – 400 IU NR/day pn.	1420	9.66
35 + 0			720 IU/day	720	
35 + 1			520 IU/day	520	
35 + 2			480 IU/day	480	
35 + 3	155	59	60 IU/day	60	0.39
35 + 4			0 IU/day	0	
35 + 5			0 IU/day	0	
35 + 6			0 IU/day	0	
36 + 0			0 IU/day	0	
36 + 1 (cesarean section)			0 IU/day	0	

Investigation

Results of blood samples are shown in Table 2. The patient was severely insulin resistant with a non-fasting C-peptide concentration of 3294 pmol/L (reference range 370–1470 pmol/L) and an extremely high level of proinsulin of 302 pmol/L (reference range 2.1–13 pmol/L). Leptin and MBL levels were also high as was the level of IGF-1 (401 µg/L; reference range 69–227 µg/L), but it corresponded to third-trimester levels of IGF-1 in pregnant women without diabetes (3). Inflammatory markers adiponectin, cytokines (interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) and high sensitive CPR (hsCRP) were comparable to other women with gestational diabetes (GDM) in late pregnancy (4), whereas fibroblast growth factor 21 (FGF-21) levels were relatively low. CRP was mildly elevated, which is a typical feature of PCOS, and free fatty acids (FFA) were low due to the high doses of exogenous insulin administration. CD 163, cortisol and standard biochemical profile, including lipid profile, was unremarkable and antibodies against insulin were undetectable. The patient gave written informed consent to have coding exons and introns of the INSR gene examined, but no mutations were detected.

The development in HbA1c during pregnancy is shown in Fig. 1B, and as the target HbA1c for pregnant women with diabetes in Denmark is 6.5% (48 mmol/mol) before gestational week 20 and 5.6% (37 mmol/mol) after week 20, the patient was never optimally controlled during pregnancy, despite the frequent increase in insulin doses. Although the patient was advised not to gain more than 0–5 kg during pregnancy, she gained 40 kg from 115 kg prior to pregnancy to 155 kg, and the weight gain coincided with the increase in insulin requirements as shown in Fig. 1.

Treatment

The specific increase in insulin doses are outlined in Table 1. Diabetes regulation was managed by self-monitoring of glucose seven times a day, and frequent insulin adjustments were performed in close collaboration with endocrinologists, aiming at capillary plasma glucose levels of 4–6 mmol/L preprandial and 4–8 mmol/L 1½ h after meals. Dietary advice, caloric restriction and exercise recommendations were given along with insulin treatment.

Outcome and follow-up

At week 36+1 a healthy baby was delivered by cesarean section. Apgar scores at 1, 5 and 10 min were normal, and

Table 2 Hormones and inflammatory markers.

Gestational age (week + days)	**35 + 3**	**35 + 4**	**35 + 5**	**2 days pp**	**7 months pp**
P-Insulin (18–173 pmol/L)	923	1295	228	76	258
C-peptide (370–1470 pmol/L)	3294		1623	1275	1836
P-proinsulin (2.1–13 pmol/L)	102	177			76
Insulin antibody (<10 negative)	4				
Prolactin (90–580 × 10^{-3} IU/L)	5280		4787		100
IGF-1 (69–227 µg/L)	401			123	146
P-cortisol (171–536 nmol/L)	377				375
CRP (<8.0 mg/L)	14				
CD163 (0.69–3.86 mg/L)	2.02				
Adiponectin (mg/L)	7.70				
FFA (mmol/L)	0.46				
hsCRP (mg/L)	10.2				
MBL (ng/mL)	2418				
IL-6 (pg/mL)	1.48				
TNF-α (pg/mL)	6.91				
Leptin (µg/L)	117.6				
FGF-21 (ng/L)	181.2				

IGF-1, insulin-like growth factor; FFA, free fatty acids; hsCRP, high sensitive CRP; MBL, mannan-binding lectin; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; FGF-21, fibroblast growth factor 21.

the baby had no abnormalities. The birthweight was 3850 g, large for gestational age with a z-score of 3.05, and the blood glucose was 2.8 mmol/L 1 hour1 h after delivery, and 4.3 mmol/L 4 h after delivery, compatible with no neonatal hypoglycemia. Placental weight was 920 g. Mother and baby were discharged from the hospital 5 days after delivery, and the patient was advised to continue self-monitoring of glucose regularly and consult her general practitioner for diabetes check-up.

Shortly after delivery, blood glucose, plasma insulin, C-peptide and IGF-1 normalized and as the patient was breastfeeding, she did not receive any antidiabetic medication. Seven months post-partum, insulin, C-peptide and proinsulin had increased above reference range and HbA1c was 116 mmol/mol, indicating that insulin resistance had returned and that treatment was warranted.

Discussion

We report a rare and clinically difficult case of extreme insulin resistance with daily insulin requirements of ~1500 IU/day during pregnancy in an obese woman with T2D and PCOS. To our knowledge, such a case has never been described in the literature before.

First of all, it is relevant to raise the question: did the patient really take ~1500 IU/day? As the patient's therapists, we do not have any reason to believe the opposite. We had close contact with the patient at least once a week, where insulin doses were verified by the patient and adjusted according to blood glucose profiles. The patient seemed compliant and collection of insulin pens at the pharmacy was confirmed in the prescription database. The high levels of insulin measured in the blood samples also confirmed that the patient was compliant.

Secondly, why did the patient get so insulin resistant? The determinants and causal mechanisms of insulin resistance in pregnancy are complex and still not completely revealed (5), but it is well-known that obesity and PCOS, factors that were predominant, in this case, are strongly associated with insulin resistance. The massive weight gain, in this case, is especially important, given that it induces insulin resistance, which in turn leads to higher insulin requirements and consequent weight gain, creating a vicious cycle. Additionally, the patient was previously diagnosed with T2D, where insulin resistance is an important part of the pathophysiology.

The changes in insulin sensitivity during pregnancy are also believed to be caused partly by hormones, cytokines and adipokines from the placenta, but no single hormone has been found to explain the insulin resistance in pregnancy.

In the present case, we measured different hormones and cytokines (Table 2) and found that IGF-1, leptin and MBL were abnormally high. Hyperleptinemia is a result of an increased synthesis and secretion from abundant adipose tissue (6), but leptin is also secreted in the placenta and leptin levels increase substantially during pregnancy. McIntyre *et al.* conclude that maternal insulin sensitivity in pregnancy is positively associated with leptin and the growth hormone axis (7), and as these parameters were

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very high in the present case, they might account for the extreme insulin resistance.

MBL plays a role in the immune system as it activates the complement system and has been linked to diabetic nephropathy and the risk of cardiovascular disease in diabetes (8, 9). MBL levels increase up to 140% during pregnancy with a sharp decrease after delivery (10) and is speculated to contribute to a normal placentation and pregnancy. However, previous studies have found, that serum MBL levels are positively related to insulin sensitivity in women with PCOS (11) and can therefore not explain the severe insulin resistance in our case.

Only very few cases exist on extreme insulin resistance in pregnancy. One other case describes a woman with insulin requirements of daily doses up to 480 IU/day. The reason for the insulin resistance was a heterozygous ΔLeu^{999} mutation found in the INSR gene, and treatment with metformin reduced the insulin requirements substantially to 150 IU/day in the following pregnancy (12). Although there were no mutations found in the INSR gene in our case, metformin could have been added in order to spare insulin by sensitizing insulin action through suppressing hepatic glucose output or increasing glucose uptake in peripheral tissues. However, although metformin is considered safe in pregnancy (13), it is not recommended for pregnant women in Denmark and is therefore only used in very rare cases.

It would also have been worth considering using high concentrate insulin (insulin degludec 200 IE/mL or insulin glargine 300 IE/mL), but these insulin products are mostly used for patients with type 1 diabetes and a change to another type of insulin during pregnancy could potentially lead to unwanted excursions in blood glucose levels. Moreover, results from ongoing studies using high concentrate insulin in pregnant women with diabetes are pending. A retrospective study has however shown improved glycemic control in pregnant women with severe insulin resistance when using 500 IU/mL concentrated insulin (14), but this type of insulin is not available in Denmark. The great challenge in the current case was the continuous increase in insulin requirements and the balance between hypo- and hyperglycemia. One could speculate if very high doses of insulin have any clinical effect. A previous dose–response study in severely insulin-resistant patients with T2D, however, showed that a dose–response relationship to insulin is maintained at very high doses and it thus seems reasonable to increase insulin doses in these patients in order to accomplish optimal glycemic control (15). The patient in the present case did not accomplish optimal control, based on the HbA1c measurements, despite the extremely large doses of insulin, and at delivery, the baby was large for gestational age, but did not suffer from hypoglycemia.

Also, the patient did not experience episodes of hypoglycemia until GA 35+0, where insulin requirements suddenly declined rapidly and the patient had to reduce insulin doses substantially, ending up with no insulin requirements the last 5 days prior to delivery. The reason for this rapid decline remains unclear, as there were no signs of placental insufficiency or lipohypertrophia at the injection sites. Nevertheless, the rapid and dramatic changes in insulin requirements led to the induction of labor to foreclose that a potential placental insufficiency had consequences for the fetal well-being.

Conclusion

Insulin resistance during pregnancy is accentuated in situations with diabetes, PCOS, obesity and inactivity and can become severe. We experienced a therapeutic challenge in a pregnant women with a history of PCOS, obesity and T2D with extreme needs for exogenous insulin, but through a close collaboration between patient, obstetricians and endocrinologists a successful outcome was obtained. Metformin might potentially have reduced insulin doses, but is considered experimental in Denmark and was therefore not attempted.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement
U K, P O and J F collected data. U K wrote the manuscript. U K, P O, N M and J F were in charge of the patient treatment and P O, N M and J F contributed to the manuscript.

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