New onset Addison's disease presenting as prolonged hyperemesis in early pregnancy

Nasilone wymioty jako nowy objaw rozwijającej się choroby Addisona we wczesnej ciąży

Lewandowski Krzysztof[1], Hincz Piotr[2], Grzesiak Mariusz[2], Cajdler-Łuba Agata[1], Salata Ireneusz[1], Wilczyński Jan[2]*, Lewiński Andrzej[1]*

[1] Departments of Endocrinology, Diabetes & Metabolic Diseases, "Polish Mother" Memorial Research Institute and the Medical University of Lodz, Poland
[2] Department of Feto-Maternal Medicine, Research Institute "Polish Mother's Memorial Hospital" and the Medical University of Lodz, Poland

*Wilczyński J and Lewiński A are joint senior last authors

Abstract

A 32-year old Caucasian was admitted at 14 weeks of gestation with hypotension and weight loss. Family members noted that she appeared "tired" prior to pregnancy.

Past medical history included primary hypothyroidism treated with thyroxine (100μg/day). She had a healthy daughter aged 2.5 years who had been born small for gestational age. At about 8 weeks of gestation she started to vomit several times a day. She was treated with antiemetics and intravenous fluids. Following discharge she remained nauseated, weak and lightheaded and lost about 8 kg of weight. After readmission she appeared ill and dehydrated, BMI 16.6 kg/m², BP 90/60 mmHg supine, 70/50mmHg upright (with faint-like sensation), normal heart sounds, chest clinically clear, abdomen soft and not tender.

Investigations revealed severe hyponatraemia (sodium 112mmol/L), normal potassium level 4.3mmol/L, normal renal function, TSH 1.31μIU/mL (reference range (RR): 0.27-4.2), freeT4 1.99ng/dL (RR: 0.93-1.7), freeT3 3.29pg/mL (RR: 2.57-4.43), anti-TPO antibodies 467IU/mL (RR: <34)). She was hyperpigmented, hypotensive and hyponatraemic despite rehydration. Cortisol & ACTH, followed by a 250μg short Synacthen test were requested and revealed peak cortisol response of 17nmol/L (RR: above 550nmol/l) as well as high baseline ACTH (969pg/mL, RR: 0-46pg/mL). She was started on hydrocortisone and felt tremendously better. A diagnosis of Addison's disease was made (in view of hypothyroidism as a part of Autoimmune Polyglandular Syndrome type II). She was discharged on hydrocortisone and fludrocortisone replacement. Further during her pregnancy there was about two-week foetal growth delay. She, however, delivered a healthy female infant at 36 weeks of gestation.

Conclusions: *New onset Addison's disease is rare in pregnancy, but may present with prolonged vomiting and weight loss. Therefore adrenal failure should be included in the differential diagnosis of hyperemesis gravidarum.*

Key words: **Addison disease** / **autoimmune polyglandular syndrome type II** / / **pregnancy** / **hyperemesis gravidarum** /

Adres do korespondencji:
Piotr Hincz
Department of Feto-Maternal Medicine, „Polish Mother" Memorial Research Institute
and the Medical University of Lodz, Poland
Rzgowska 281/289, 93-338 Lodz, Poland
Phone: +48 (42) 271-13-13
E-mail: piotr.hincz@umed.lodz.pl

Otrzymano: **05.02.2010**
Zaakceptowano do druku: **20.06.2010**

Streszczenie

32 letnia kobieta rasy kaukaskiej została skierowana do szpitala z powodu hipotensji i utraty masy ciała. Jej członkowie rodziny zwracali uwagę na fakt, że w okresie poprzedzającym ciążę często zgłaszała uczucie zmęczenia i znużenia. W przeszłości rozpoznano u niej pierwotną niedoczynność tarczycy i była leczona tyroksyną (100µg/dobę). Pierwsza ciąża została zakończona urodzeniem noworodka z rozpoznaną hipoptrofią, którego dalszy rozwój przebiegał prawidłowo.

W obecnej ciąży od ósmego tygodnia ciąży rozpoczęły się nasilone wymioty. U ciężarnej zastosowano leki przeciwwymiotne oraz dożylną suplementację płynową. Pomimo zastosowanego leczenia nadal obserwowano uporczywe wymioty, osłabienie i znaczną utratę masy ciała (około 8 kilogramów). Po ponownej hospitalizacji stwierdzono nasilenie objawów chorobowych, znaczne osłabienie i odwodnienie, BMI 16,6kg/m², ciśnienie krwi tętnicze 90/60mmHg w pozycji leżącej, 70/50mmHg w pozycji stojącej z następową hipotonią ortostatyczną. W badaniu fizykalnym tony serca czyste, akcja serca miarowa, szmer pęcherzykowy prawidłowy, brzuch miękki, niebolesny. W badaniach laboratoryjnych stwierdzono hiponatremię (sód 112mmol/L), potas 4,3mmol/L, prawidłowe wykładniki funkcji nerek, TSH 1,31µIU/mL (wartości referencyjne (WR): 0,27-4,2), fT4 1,99ng/dL (WR: 0,93-1,7), fT3 3,29pg/mL (WR: 2,57-4,43), przeciwciała anty-TPO 467IU/mL (WR: <34)).

U ciężarnej stwierdzono wzmożoną pigmentację skóry oraz hipotonię i hiponatremię narastającą pomimo zastosowanej suplementacji objętościowej i elektrolitowej. Oznaczono stężenie kortyzolu i ACTH.

Następnie wykonano krótki test z użyciem 250µg synacthenu. Uzyskano szczyt wyrzutu kortyzolu 17nmol/L (WR: above 550nmol/l) jak również stwierdzono wysoką wartość wyjściową ACTH (969pg/mL, WR: 0-46pg/mL). Rozpoczęto terapię z wykorzystaniem hydrokortyzonu uzyskując znaczącą poprawę. W oparciu o objawy niedoczynności tarczycy jako części Wielogruczołowego Zespołu Autoimmunologicznego typu II postawiono rozpoznanie choroby Addisona. Ciężarną wypisano z zaleceniem terapii uzupełniającej hydrokortyzonem i fludrokortyzonem. W dalszym przebiegu ciąży odnotowano dwutygodniowe zahamowanie wzrostu płodu a ciąża została zakończona w 36 tygodniu porodem zdrowej dziewczynki.

Wnioski: *Wystąpienie choroby Addisona jest rzadkością w przebiegu ciąży i może być manifestowane przedłużającym się okresem wymiotów oraz utratą masy ciała. W przypadku wystąpienia takich objawów w diagnostyce różnicowej należy zatem zawsze uwzględnić niewydolność nadnerczy.*

Słowa kluczowe: **choroba Addisona** / **wielogruczołowy zespół autoimmunologiczny typu II** / **ciąża** / **wymioty ciężarnych** /

Introduction

Before the advent of steroid treatment Addison's disease was associated with very high mortality regardless of age of diagnosis. The early series of Addison's disease in pregnancy report a 35% mortality rate [1]. Despite, however, advances in clinical medicine, Addison's disease still constitutes a serious medical condition that poses several problems for diagnosis and treatment. We present the case of a case of autoimmune polyglandular syndrome type 2, where Addison's disease developed *de novo* in pregnancy and so initially caused significant diagnostic problems.

Case description

A 32-year old Caucasian was admitted at 14 weeks of gestation with hypotension and weight loss. Family members noted that she appeared "tired" prior to pregnancy. Past medical history included primary hypothyroidism treated with Thyroxine (100µg/day). Her mother had also been hypothyroid on Thyroxine replacement.

Social history: She was married and had a healthy daughter aged 2.5 years who had been born small for gestational age. She did not smoke and did not consume alcohol in excess.

At about 8 weeks of gestation she started to vomit several times a day and after each meal. This was initially thought to represent *hyperemesis gravidarum*. She was admitted to hospital and treated with antiemetics and intravenous fluids.

Following discharge she remained, however, nauseated, weak and lightheaded. Furthermore she lost about 8kg of weight over a five-week period and resumed to vomit at least once-twice day. She was re-admitted to the hospital.

Upon readmission she appeared ill, dehydrated and could not remain upright for more than few minutes. She looked hyperpigmented and admitted that her complexion was indeed darker than few months before pregnancy. Body mass index was 16.6 kg/m², blood pressure 90/60mmHg supine, 70/50 mHg upright (with faint-like sensation), normal heart sounds, chest clinically clear, abdomen soft and not tender.

Investigations revealed severe hyponatraemia (Sodium 112 mol/L), Potassium 4.3 mol/L, normal renal function, TSH 1.31µIU/mL (reference range (RR): 0.27-4.2), $FreeT_4$ 1.99g/dL (RR 0.93-1.7), $FreeT_3$ 3.29pg/mL (RR 2.57-4.43), anti-TPO antibodies 467IU/mL (RR <34)).

She remained hypotensive and hyponatraemic despite rehydration.

Endocrine consultation was requested.

Following endocrine assessment, Cortisol & ACTH, followed by a 250µg Short Synacthen test were requested.

These revealed raised ACTH and flat cortisol response to Synacthen (see Table I).

Table I. Result of intravenous administration of 250µg of synthetic ACTH (Short Synacthen test).

Synacthen Test (250µg)	0 min.	30 min.	60 min.	
Cortisol	**12**	**14**	**17**	nmol/L
ACTH	**969** [RR: 0-46]	-	-	pg/mL

**Note: Satisfactory cortisol response during short Synacthen test should be above 550nmol/L in non-pregnant subjects[2]. Reference values for pregnancy have not been defined, but are likely to be higher. This is because healthy pregnant subjects have about 60-80% increase in responses to 250µg ACTH above the non-pregnant state [3].*

Pending results of the above test she was started on Hydrocortisone (50mg tds intravenously for the first 24 hours and then 20+20+10mg orally).

Nausea and lightheadness settled and she started to feel tremendously better.

A diagnosis of Addison's disease was made (in view of coexistent Hashimoto thyroiditis possibly as a part of Autoimmune Polyglandular Syndrome type II). She had raised titre of anti-adrenal antibodies (Anti-adrenal antibodies (AAcAb): titre 1:40 (RR up to 1:10). Her anti-GAD antibodies were negative.

She was discharged on Hydrocortisone & Fludrocortisone replacement. We have decided to keep her on relatively higher steroid replacement throughout pregnancy (Hydrocortisone 15+10+5mg, Fludrocortisone 0.1 mg/day).

The further course of pregnancy had been uneventful till 26 weeks of gestation, where placental abnormalities, including multiple vacuoles and some calcifications were noted. At 30 weeks of gestation mild intrauterine growth restriction (IUGR) had been detected and it progressed in the following weeks. The intensive foetal surveillance was started and NST (non stress test) and Doppler assessment of UMB, MCA and DV were performed repeatedly. She had been hospitalized again at 34 weeks, due to IUGR (3 weeks of delay) and oligohydramnion, and 18 days later she was delivered by caesarean section. The weight of her healthy baby girl was 1950g (5-10 percentile) and she scored 8 points in Apgar scale. The reason for delivery at 36 weeks of gestation was the onset of labor (preterm leakage of amniotic fluid), while the immediate indication for cesarean section was inferred from the assessment of lower uterine segment below 2mm. There were no maternal complications in the post-partum period. Prior to discharge Hydrocortisone dose had been reduced to 15+5+5mg and Fludrocortisone to 0.05mg/day, while the dose of Thyroxine was reduced to 100µg/day at two months post-partum. The baby had moderate neonatal jaundice that was successfully treated with phototherapy. At two months postpartum the baby was well and almost doubled her birth-weight to 3.6kg

Discussion

Addison's disease still remains a serious and potentially fatal condition regardless of patient's age [4, 5]. Pregnancy results in major changes in the hypothalamo-pituitary-adrenal (HPA) axis, which in turn influence foetal growth and the timing of labor. From the beginning of the second trimester maternal cortisol secretion increases, and in late pregnancy the placenta, in large part mediated through corticotroph-releasing hormone, plays a crucial role in the regulation of the foetal HPA axis to ensure the synchronization of the various processes involved in parturition [6].

Though there are literature data on the management of previously diagnosed Addison's disease in pregnancy, the development of a new-onset Addison's disease during pregnancy is reported to be a very rare event. Only two cases of a new-onset Addison's disease during pregnancy had been reported up to the year 2000 [7], and to the best of our knowledge, only two further cases have been reported since then [8, 9]. Hence, to the best of our knowledge, this is the first reported case of Addison's disease diagnosed *de novo* during pregnancy in Poland. Hypoadrenalism can be difficult to diagnose during pregnancy, as it may mimic other conditions related to pregnancy, such as hyperemesis gravidarum [10]. Interestingly, Addison's disease is more likely to present post-partum rather than in pregnancy. This is because milder cases might be partially protected by transplacental passage of cortisol from foetus to mother. Primate studies showed that up to 60% of foetal cortisol is normally transmitted to the mother, representing 6.6% of total maternal cortisol under normal conditions [11]. Once the diagnosis is made, however, with careful monitoring, parenteral steroid cover for labour, a successful pregnancy should result.

Administration of slightly higher doses of Hydrocortisone as replacement therapy during pregnancy is deemed to be safe, as placenta is a rich source of the enzyme, 11b-ol-dehydrogenase, which converts hydrocortisone to cortisone, the biologically inactive 11-ketosteroid [12, 13].

Some penetration of Hydrocortisone into foetus has been, however, documented. Beitins et al. [14] investigated six pregnant women, immediately before an elective caesarean section at term, who received a continuous IV infusion of a mixture of radioactive-labeled hydrocortisone and cortisone. By measurement of the hormones in the mothers and newborns, the investigators demonstrated that most (about 75%) of the Hydrocortisone in the fetus was endogenous, whereas most of the cortisone was from the mother. This implies that that up to 25% of administered Hydrocortisone may reach the foetus.

Studies on use of Fludrocortisone during pregnancy have not been done in humans. FDA considers Fludrocortisone as Pregnancy Category C. Adequate animal reproduction studies have also not been conducted with Fludrocortisone acetate. However, many corticosteroids have been shown to be teratogenic in laboratory animals at low doses. Teratogenicity of these agents in humans has not been demonstrated. Manufacturer recommends that Fludrocortisone acetate should be given to a pregnant woman only if clearly needed [15].

In view of the severity of the initial presentation, as well as potentially fatal consequences of undertreated primary adrenal failure, we consider Addison's disease to represent such a case. Furthermore, in our opinion, this approach has been vindicated as our patient delivered a small-for-gestational age, but otherwise healthy girl, without any features of adrenal suppression.

No reports describing the excretion of exogenous Hydrocortisone or cortisone into human milk have been located. It is unlikely, however, that these agents pose a risk to a nursing infant. Prednisone, a corticosteroid more potent than hydrocortisone, is excreted in trace amounts into milk and is classified as compatible with breast feeding [16]. There are no data on the excretion of Fludrocortisone into human milk, however, problems in humans have not been documented. It is recommended, however, that infants born of mothers who have received substantial doses of Fludrocortisone acetate during pregnancy should be carefully observed for signs of hypoadrenalism [17].

Conclusion

New onset Addisson's disease is rare in pregnancy, but may present with prolonged vomiting and weight loss. Therefore adrenal failure should be included in the differential diagnosis of *hyperemesis gravidarum*.

References

1. Cohen M. Addison's disease complicated by toxemia of pregnancy. *Arch Intern Med.* 1948, 81, 879-887.
2. Agha A, Tomlinson J, Clark P, [et al.]. The Long-Term Predictive Accuracy of the Short Synacthen (Corticotropin) Stimulation Test for Assessment of the Hypothalamic-Pituitary-Adrenal Axis. *J Clin Endocrinol Metabol.* 2006, 91, 43–47.
3. Nolten W, Lindheimer M, Oparil S, [et al.]. Desoxycorticosterone in normal pregnancy. Sequential studies of the secretory patterns of desoxycorticosterone, aldosterone, and cortisol. *Am J Obstet Gynecol.* 1978, 132, 414-420.
4. Bird S. Failure to diagnose: Addison disease. *Aust Fam Physician.* 2007, 36, 859-861.
5. Flakiewicz-Kula A. Ciąża i poród w przebiegu choroby Addisona. *Ginekol Pol.* 1978, (49), 643-646.
6. Trainer P. Corticosteroids and pregnancy. *Semin Reprod Med.* 2002, 20, 375-380.
7. Glazier M, Waldron W. An unusual cause of postpartum vomiting. *Arch Fam Med.* 2000, 9, 284-286.
8. Scrimin F, Panerari F, Guaschino S. Addison's disease and hypothyroidism untreated until twenty-four weeks of pregnancy. *Acta Obstet Gynecol Scand.* 2005, 84, 198-199.
9. Fux Otta C, Szafryk de Mereshian P, Iraci G, [et al.].Pregnancies associated with primary adrenal insufficiency. *Fertil Steril.* 2008, 90, 1199.e17-20.
10. Ozdemir I, Demirci F, Yücel O, [et al.]. A case of primary Addison's disease with hyperemesis gravidarum and successful pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2004, 113, 100-102.
11. Drucker D, Shumak S, Angel A. Shmidt's syndrome presenting with intrauterine growth retardation and postpartum addisonian crisis. *Am J Obstet Gynecol.* 1984, 149, 229-230.
12. Murphy B, Clark S, Donald I, [et al.]. Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. *Am J Obstet Gynecol.* 1974, 118, 538–541.
13. Levitz M, Jansen V, Dancis J. The transfer and metabolism of corticosteroids in the perfused human placenta. *Am J Obstet Gynecol.* 1978, 132, 363–366.
14. Beitins I, Bayard F, Ances I, [et al.]. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. *Pediatr Res.* 1973, 7, 509–519.
15. *Florinef product monograph* (Squibb-Canada), Rev 10/26/77, Rec 7/14/89.
16. Venkataraman M, Shanies H. Pregnancy and asthma. *J Asthma.* 1997, 34, 265–271.
17. Florinef (Squibb). In: *Compendium of pharmaceuticals and specialties.* 23rd. Ed. Krogh C. CPS Ottawa: Canadian Pharmaceutical Association. 1988, 337-338.