

Unassisted successful pregnancy in a case of Addison's disease with recurrent pregnancy loss

Sir,

Pregnancy itself is a state of physiological hypercortisolism. Due to increased production and secretion, plasma cortisol levels increase progressively starting in the first trimester. The half-life of serum cortisol is prolonged, and by term usually the circulating cortisol levels are 2- to 3-fold higher than those in nonpregnant women.^[1] Therefore, recognizing adrenal insufficiency in the pregnant women is not straightforward. Adrenal insufficiency in pregnancy is associated with substantial mortality and morbidity, if not treated and/or diagnosed early in the course of gestation.^[2,3] Fetal growth restriction, oligohydramnios, and fetal distress have all been linked to inadequately treated maternal Addison's disease.^[4,5]

Cortisol secretion and metabolism are decreased in patients with both primary and secondary hypothyroidism.^[6] The magnitude of the changes in secretion and metabolism is, however, similar to that of serum cortisol concentrations, but urinary cortisol excretion is normal.^[7] Thyroid hormone stimulates the activity of hepatic $\Delta 4$ 5-steroid reductases, and it decreases the reductase activity of hepatic 11 hydroxysteroid dehydrogenase (11 HSD) type 1, thereby decreasing conversion of cortisone, which is biologically inactive, to cortisol.^[8-10] The activity of 11 HSD type 1 reductase activity is increased in overtly hypothyroid patients causing increased cortisone conversion to cortisol with a consequent decrease in the ratio of tetrahydrocortisone to tetrahydrocortisol in urine.^[11] Theoretically, occurrence of hypothyroidism in a case adrenal insufficiency may mask its severity. We report this young lady with clinically overt Addison's disease who carried this pregnancy till 8th month after seven recurrent abortions. She had supervening hypothyroidism this time, which is likely reason for alteration of cortisol metabolism. We could not find any such presentation in the published literature, to the best of our knowledge.

She was a 29-year-old female who presented in the 8th month of pregnancy with history of generalized weakness, easy fatigability, lethargy, asthenia, and progressive discoloration of the skin. Patient had history of seven recurrent first-trimester abortions in the past. Patient noticed progressive dark brown tanning of the skin for the past 9 years. On examination, patient had pallor,

puffiness of face, hyperpigmentation over face, knuckles, tongue, and buccal mucosa [Figure 1]. Vitals revealed pulse of 100 beats/minute and blood pressure was 100/60 mm Hg supine and 80/50 mm Hg standing. Patient was clinically hypothyroid with Zulewski score of 8. She had no thyromegaly. She had 32 weeks gravid uterus with cephalic presentation and fetal heart rate of 135 beats/minute. Rest of the general and systemic examination was unremarkable. There were no clinical pointers to any overt cause for bad obstetric history except features of Addison's disease. Investigative workup revealed normal hemogram, kidney function, liver functions, serum calcium, lipid profile, LDH, CPK, and electrolytes. Thyroid function test revealed free T4 of 1.26 ng/dl (normal range 0.7–2.5 ng/dl) and thyroid-stimulating hormone (TSH) of 12.48 mIU/L (normal range 0.4–4.2 mIU/L). Anti-TPO antibodies levels were 600 IU/ml (normal range < 34 IU/ml). Basal cortisol level done at 8 AM was 3.78 μ g/dl (normal range > 15 μ g/dl). Antiphospholipid antibodies were negative. TORCH (toxoplasmosis, rubella, cytomegalovirus virus, herpes virus) screen was also negative.

Patient was started on oral steroids initially and levothyroxine was added later on once patient became eucortisolemic and repeat TSH was 0.48 mIU/L. Patient was maintained on the same treatment till the time of delivery, when patient was put on IV steroids. Patient delivered by normal vaginal delivery and postpartum period was uneventful though on levothyroxine 100 μ g/day and prednisolone 5–7.5 mg/day. Six weeks after delivery, steroids were stopped for 24 hours and 8 AM cortisol was repeated, which was 6.4 μ g/dl. Adrenocorticotrophic hormone stimulation test showed inadequate response to 250 μ g



Figure 1: (a) Clinical photomicrograph showing hyperpigmentation of the face. (b) Clinical photomicrograph showing hyperpigmentation of tongue. (c) Profile photomicrograph showing abdominal protuberance due to gravid uterus. (d) Clinical photomicrograph showing hyperpigmentation and dry rough skin of the hands

IV subcutaneous dose (maximum response 12.3 µg/dl). Luteinizing hormone, follicle-stimulating hormone, and prolactin levels were normal. Patient was again started on steroids and levothyroxine was continued.

Adrenal glands in pregnancy undergo hypertrophy to meet the extra stress of pregnancy which is important for the continuation of pregnancy.^[12,13] Early diagnosis of any adrenal insufficiency and prompt steroid treatment is important for uneventful fetal and maternal outcome.^[14] Early morning plasma cortisol levels of 3.0 µg/dl confirm adrenal insufficiency while a cortisol > 19 µg/dl in the first or early second trimester excludes the diagnosis in a clinically stable patient.^[15,16] Our patient was clinically and biochemically in hypoadrenal state and history was suggestive of a long duration illness. Since common causes of recurrent abortions were ruled out in our patient, the possible cause of recurrent abortions was adrenal insufficiency. The reason for successful pregnancy till 8th month was not clear. One possibility is that the patient was able to carry this pregnancy to near term due to the presence of concomitant hypothyroidism. As already described, serum cortisol concentration in a normal eucortisolemic person does not change with the development of hypothyroidism.^[7] However, the effect of hypothyroidism on serum cortisol concentration in a patient with adrenal insufficiency is not known. Thyroxine treatment in a patient with underlying adrenal insufficiency may precipitate adrenal crisis as does a major stress in the form of surgery, sepsis, or pregnancy.^[17] Cortisol in physiological doses itself exerts an inhibitory effect on serum TSH levels.^[18,19] Also in supraphysiological doses, it inhibits peripheral conversion of T₄ to T₃.^[20] Glucocorticoid treatment in our patient did not result in normalization of TSH. Patient was therefore started on thyroxine replacement. The other explanation to this success could be enough fetal cortisol production because it may be adequate enough to protect mother from severe adrenal insufficiency until postpartum.^[21]

This mechanism was, however, unlikely in our patient, because patient was in hypoadrenal state and previously all the pregnancies were first-trimester abortions.

In conclusion, this patient was documented to have adrenal insufficiency and hypothyroidism both at presentation and after delivery. Despite having recurrent abortions in the past, patient was able to carry this pregnancy to near term. The possible reasons could be (1) a concomitant hypothyroid state, (2) enough fetal cortisol production, or (3) both. We report this patient because of unusual clinical presentation as there is no such presentation reported in the literature till date.

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