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Case Report

Late onset congenital adrenal hyperplasia in pregnancy

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ABSTRACT

Congenital adrenal Hyperplasia (CAH) is a rare disorder to manage in pregnancy as CAH is known to cause infertility. Late onset CAH is more so with 21-hydroxylase deficiency being the most common enzyme deficiency for the same. The mainstay of management in pregnancy is multidisciplinary team management with a consultant Obstetrician and Medical Endocrinologist, steroid treatment and avoiding virilisation of the female patient in early pregnancy is important continuation of dexamethasone is controversial with conflicting evidence and also precipitating or worsening hyperemesis in pregnancy.

1. Background

Congenital adrenal hyperplasia (CAH) is a disorder with is autosomal recessive in nature. It is caused by deficiency of enzymes which are precursors for cortisol and aldosterone which are precursors for sex hormone synthesis. The most common enzyme deficiency seen is the 21 hydoxylase deficiency followed by deficiency of enzyme 11 beta hydroxylase followed by very rare mutation deficiencies of 3 beta hydroxysteroid dehydrogenase 2, 17 alpha hydroxylase and cholesterol side chain cleaving enzyme among many more.

Depending on the enzyme deficiency produced by the specific allele that the patient has some alleles result in a spectrum of severe degrees of symptoms to a mild form of disease.

Deficiency of 21 hydroxylase enzyme, which catalyzes conversion of 17- hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycortisone respectively are precursors in the hormone synthesis of cortisol and aldosterone. The synthetic block in cortisol will lead to corticotropin stimulation of the adrenal cortex and resulting in accumulation in cortisol precursors that are diverted to sex hormone synthesis.

Congenital adrenal hyperplasia is divided into classic congenital adrenal hyperplasia that includes salt wasting (SW), simple virilising (SV) and non classical disease. The severity of classical congenital adrenal hyperplasia is based on the amount of deficiency of 21 hydroxylase enzyme. Classical congenital adrenal hyperplasia with associated <5% activity of 21 hydroxylase enzyme is associated with simple virilizing type.

The most severe form of classical congenital adrenal hyperplasia is salt- wasting congenital adrenal hyperplasia and this is due to complete loss of 21 hydoxylase enzyme activity.

Several authors have reported an increase infertility among women in case reports and smaller case series.[1–5] Excess androgen can inhibit folliculogenesis of the ovaries and elevated progesterone levels can cause persistent inhibition of follicular growth and endometrial proliferation, failure of endometrial breakdown and impermeability of cervical mucus is the mechanism for decreased fertility in patients with congenital adrenal hyperplasia.[6]

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If corticosteroid supplementation is insufficient, androgen production from adrenals will increase and suppress gonadotropin secretion from the pituitary leading to disturbances in the ovarian cycle leading to anovulation and infertility.

Disturbance in ovarian function can also occur by ovarian adrenal tumours displacing normal tissue in the ovary and producing steroids.[7]

Improving fertility outcomes and decreasing fetal exposure to androgens is by optimal glucocorticoid therapy, targeting lowering of ACTH levels, decreasing androgen and progesterone levels and ovarian adrenal rest tumour size. Early diagnosis and treatment with steroids, appropriate vaginal opening for coitus and sufficient suppression of adrenals during attempts at pregnancy is required.

Need for steroids during pregnancy varies, with hydrocortisone and prednisolone being the drugs of choice and dexamethasone not being recommended as this drug is able to cross the placenta and causes changes in the fetus. However when the fetus is at risk for developing congenital adrenal hyperplasia, dexamethasone 20 microgram/kg/day in 3 divided doses is given to pregnant women, ideally before 7 weeks of gestation as this inhibits the fetal hypothalamic pituitary adrenal axis and excess androgen secretion prevents virilisation of the affected female fetus.[8] However this is not recommended by the Endocrinology society 2010 practice guideline as they still consider it experimental due to varied outcomes in reviewed data.[9]

2. Case Presentation

A 31 year old Caucasian lady, conceived spontaneously, with diagnosed CAH secondary to 21 hydroxylase deficiency 6 years ago was referred to antenatal clinic at Stepping Hill Hospital, Stockport which is a district general hospital at 7 weeks gestation by the GP for the same. This was her third pregnancy and she had two previous miscarriages in 2013. She was not on any treatment for congenital adrenal hyperplasia at the time of pregnancy referral and had symptoms of facial hirsuitism and precocious puberty with appearance of secondary sexual characters, telearche and pubarche at around of the age of ten but had a normal menarche at age 13 years. Periods regular. She had been diagnosed with congenital adrenal hyperplasia in 2013 and was given steroids (dexamethasone) and discharged after a year. She does not note any stressful significant event in her life which may have precipitated any adverse events.

Her family history of significance was that her half sister has salt wasting congenital adrenal hyperplasia and is on treatment with steroids currently 16 years old.

She was started on low dose Asprin 150mg at night and was followed up antenatally in the diabetes/ endocrine pregnancy joint clinic in Stepping Hill Hospital, Stockport. Dexamethasone was continued in second trimester.

A plan was also made to contact the district genetics department and to test the patients partners carrier status for the same. Partner had been investigated for the BRACA gene and also been screened for congenital adrenal hyperplasia at the same time and was quoted at less than 1 in 325 chances for the baby to have a problem based on genetic studies.

Correspondence with her doctors from the Christies Hosptial, Manchester stated that we could consider 100mgs hydrocortisone intravenously at the time of labour or delivery to prevent adrenal crisis. This had later been discussed with the patient by the consultant endocrinologist at Stepping Hill Hospital who considered that the hydrocortisone might have been over medicalisation but had no objections of having 100mg intravenous hydrocortisone if she requires during an emergency caesarean section and could have 50mg of hydrocortisone intramuscularly during prolonged labour and also recommended that she have an anesthetic review just to plan things through. The endocrinologist didn't think there was also any benefit of providing Asprin for this patient in this pregnancy.

Patient was regularly reviewed in antenatal clinic and had an induction of labour for large for gestational age baby at 40 weeks gestation. Induction was begun with an outpatient induction with a 10mg propess (PGE2) insertion on the antenatal day care unit and patient was asked to come in if she had any signs or symptoms of going into labour like, cervical mucus plug loss (show) any start of intermittent gradually progressive abdominal or backache, per vaginal loss of fluid (spontaneous rupture of membranes or blood loss). Since there were no signs of labour, patient was then brought in for inpatient induction and had three doses of prostin which is PGE2 gel (1-2 mg) for induction. Due to failed propess induction and prostin as well, patient opted to have a caesarean section instead of another cycle of PGE2 gels after a rest day. Intraoperatively there were no complications from an obstetric point of view in terms of bleeding and placental site estimated blood loss was 300mls. Delivered a female baby cried immediately after birth with good APGARs. Patient was also given 100mg hydrocortisone intraoperatively during the caesarean section as well. Patients observations (heart rate, blood pressure, saturation, blood loss, input and output) were monitored closely postoperatively in a recovery room. After all observations were stable over the post operative period patient was shifted to the postnatal ward where the recovery was uneventful.

2.1. Investigations

Blood investigations and endocrinology test for 21 hydroxylase enzyme deficiency suggests that high concentrations of progesterone and 17 hydroxy progesterone in blood is significant on deciding the

effect of treatment as progesterone blocks the conversion to 11 deoxy cortisol. Baseline investigations for hormones were done at endocrinology clinic visit at 17 weeks serum progesterone was – 156nmol/l serum cortisol was -550 serum ACTH- 22ng/l (which was normal) Serum 17-hydroxy progesterone was 31.8nmol/l (which was raised but well within range for not requiring steroid suppression). HbA1C was normal and this was tested as patients with CAH have hypo glycemia due to hypo cortisolism. All other full blood count, electrolytes, liver and kidney function tests have been normal throughout pregnancy. From an obstetric point of view her scans had all been normal. Placental site was away from the cervical os. Except for the last ultrasound done in the third trimester which showed an LGA baby with an estimated fetal weight of 3633g and plotting on the 90^{th} centile and hence had to be induced to be delivered 40 weeks of gestation.

2.2. Outcome and Follow-Up

Patient reviewed postnatally on day 2 wound healthy, pv bleeding minimal, and moving bowels and bladder prior to discharge. No obstetrically indicated follow up was required in this case as she was asymptomatic throughout pregnancy and immediate puerperium.

3. Discussion

The number of women with CAH desiring pregnancy and actively trying to conceive according to literature is around 20%.[4] In women with CAH pre pregnancy counselling and steroid replacement and monitoring should be done several years prior to conception and pregnancy. Explanation regarding reduced fertility outcomes need to be explained to the patient as well.[10]

Congenital adrenal hyperplasia was first described by DeCrecchio in 1865 and was later confirmed by Wilkins et al in 1951.[11]

Literature as reported that mechanism of decreased fertility is by effect of progesterone on the gonadotropic axis. Bachelot et al also demonstrated that the best predictor of LH pulsatility in CAH is hormonal control. Importance of careful monitoring and suppression of progresterone to control and regulate the menstrual cycle an optimise fertility.[12] But sometimes even with excessive glucocorticoid doses it is difficult to supress progesterone and 17-OH- progesterone concentration.[13,14]

After conception it is recommended to use steroids such as prednisolone, prednisone and hydoxycortisone which can be metabolised by placental hormone 11b hydroxysteroid dehydrogenase type 2 rather than dexamethasone as this is not inactivated by the placenta. Casreras et al[4] suggested that prednisolone 2-5mg every 8 hours to aim for a progesterone level less than 63ng/dl is recommended.

Once pregnant the woman might need an increase in steroid doses during pregnancy depending on the hormonal levels but excessive doses of glucocorticoid also put the women at risk of fluid overload, cushingoid features, weight gain, hypertension and hyperglycemia.[10] Steroid replacement monitoring during pregnancy is challenging due to confounding factors such as sex hormone binding globulin or other hormones affecting the assay specificity. It is recommended to use laboratories with expertise in steroid immunoassay and comparing the results with laboratory-specific reference values in pregnancy.[2]

Placental tissue in humans serve as a metabolic barrier in reducing fetal exposure to circulating maternal androgens and androgen precursors. As discussed earlier dexamethasone has been controversially used to treat affected female fetuses in these cases in preventing virilisation with the goal of reducing feminising gential reconstructive surgery. But treatment with dexamethasone does pose some ethical issues of gender assignment as well.[9]Depending on any reconstructive genital surgery being performed mode of delivery needs to be looked into-whether the patient is not suitable for vaginal delivery and requires an elective caesarean section. Date that is available does not support glucocorticoid usage with spontaneous miscarriage in classical congenital adrenal hyperplasia, it also does not support any evidence of subsequent trophoblastic disease and steroid use.

In this pregnancy with the diagnosis and treatment of CAH being later on in the patients life, receiving steroid therapy and then spontaneously conceiving being monitored for any symptoms and hormonal assays of congenital adrenal hyperplasia, having follow up in consultant led antenatal clinic with a joint endocrinology pregnancy clinic helped to manage this pregnancy. The only point of time the woman required glucocorticoids was during her caesarean section. And thus had a very uncomplicated antenatal, intrapartum and postnatal care.

4. Learning points/Take home Messages

Congenital adrenal hyperplasia in pregnancy requires a multidisciplinary approach due to complexities which arise in its management. Requirement of an obstetrician, pediatrician, geneticist and endocrinologist.

Fertility outcomes improve with adequate dosing of steroids prior to conception.

Prior to conception the optimal steroid dose should target suppression of progesterone levels if elevated during the follicular phase of the menstrual cycle.

Hormonal assays during pregnancy is important for glucocorticoid suppression/ treatment.

Mode of delivery, requirement of steroid doses during any prolonged labour / caesarean section needs to be tailored to the needs of the patient as well, obstetric risk factors must also be taken into account separately.

Progesterone levels especially if elevated play an important role in requirement of steroids for suppression dosing during antenatal and intrapartum care.

In pregnancies with unaffected fetuses the placenta plays a very important role as a metabolic barrier to reduce fetal exposure to circulating maternal androgens.

5. Summary

A 31 year old lady diagnosed with mild congenital adrenal hyperplasia with 21 hydroxylase deficiency was seen in antenatal clinic and managed in a consultant led unit of joint endocrinology pregnancy clinic in her pregnancy. As she was diagnosed just 6 years before she became pregnant and was on steroid treatment for the same she had no complicating issues during pregnancy and did not receive any steroid therapy antenatally, she was followed up routinely with all her ultrasound scans in antenatal clinic, relevant investigations were done to exclude any need for androgen or progesterone suppression and was induced at 40 weeks of gestation for purely obstetric reasons i.e large for gestational age. The patient then went on the have a failed induction and a caesarean section during which she was given hydrocortisone. There were no obstetric complications during the caesarean section and she delivered a female baby with good APGARs. She was thereafter discharged from the hospital, no specific serum hormone level bloods were required post pregnancy and no obstetric or endocrinology follow up was required.

6. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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None.

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