Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/clinicians-roundtable/diving-into-the-treatment-guidelines-for-congenital-adrenal-hyperplasia/26277/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Diving into the Treatment Guidelines for Congenital Adrenal Hyperplasia

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Neurocrine Biosciences Inc. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinicians Roundtable* on ReachMD, and I'm Dr. Charles Turck. Joining me today to discuss the current treatment guidelines for congenital adrenal hyperplasia, or CAH for short, is Dr. Ahmed Khattab. He's an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology at the Rutgers University Robert Wood Johnson Medical School's Child Health Institute of New Jersey. Dr. Khattab, thanks for being here today.

Dr. Khattab:
Thank you for having me.

Dr. Turck:
So to get things started, Dr. Khattab, the most recent Endocrine Society Clinical Practice Guidelines recommend maintenance therapy with hydrocortisone for growing patients with classic CAH. I was wondering if you would tell us a little bit more about that?

Dr. Khattab:
The goal of treatment in classic CAH is not just glucocorticoid replacement. We're not just replacing what's missing; however, it's also glucocorticoid suppressive therapy. We need to suppress the ACTH-driven excess androgen production using supraphysiologic glucocorticoids. So we try to administer glucocorticoids enough to suppress the ACTH-driven hyperandrogenemia, but not too much to try to avoid associated side effects of glucocorticoids. So CAH management involves a delicate balance between the risk associated with hyperandrogenism in these individuals and those risks associated with chronic glucocorticoid exposure.

To give you an example, the therapeutic targets for 17-hydroxyprogesterone are somewhere in the 100s range, 100, 200, 300, 400 nanograms per deciLitre. And this is multiples of the normal reference range. And we achieve that by a dose that's somewhere more than 12, 15, 18, 20, or even more than 20 milligrams per meter squared, which is two to three times the physiological maintenance dose in these individuals. So these individuals, or the CAH patients, are inevitably subjected to lifelong supraphysiological glucocorticoid dosing, and this does not mimic the physiological circadian rhythm of cortisol secretion.

Dr. Turck:
And when it comes to non-classical CAH, what do we need to know about the recommended use of glucocorticoid treatment in children and adolescent patients?

Dr. Khattab:
Non-classical congenital adrenal hyperplasia is a spectrum. So it could be anywhere from a non-symptomatic, asymptomatic person or individual who is diagnosed incidentally through genetic testing program, or something like a preconceptional marriage, or something like a preconceptional testing panel. Those patients, obviously a lot of them even are adults or even grownups. Or a lot of those patients are adults have completed their family number, do not have any symptoms, and clearly, they do not require treatment.

On the other end of the spectrum, there could be someone who is in the growing age, who achieves puberty a little sooner than expected, so premature adrenarche, precautious puberty those growing children may also have advanced bone age advanced

chemical maturation, which could eventually cause compromise in their final adult height. So those may be the patients where treatment may be considered.

Additionally, some females present with fertility concerns may be candidates for treatment with obviously a smaller dose of glucocorticoids than those used for classical CAH. But in summary, non-classical CAH is a huge spectrum ranging from being asymptomatic to someone who is quite symptomatic, presenting with premature adrenarche or precautious puberty, and some patients would require treatments. Others won't.

Dr. Turck:
Now turning to prenatal treatment in CAH, the guidelines don't recommend specific treatment protocols. So would you explain the rationale for why they don't and the risks and benefits associated with prenatal treatment?

Dr. Khattab:
So dexamethasone readily crosses the placenta and can suppress adrenal androgen production, and it may be administered or it has been administered to pregnant females who are suspected to be carrying a fetus affected with classical CAH. And that had to be done prior to the expected time of fetal external genitalia differentiation, sometime before the eighth or the ninth week of gestation. And that prenatal treatment would continue until term only if that fetus was confirmed to be a classical CAH-affected female. And you would confirm that by karyotyping or genotyping of fetal CYP21A2 or CAH genotyping. And that's a thing from a sample by amniocentesis or chorionic villus. And obviously, the idea is to spare the affected female the consequences of virilization of the genitalia, genital surgery, and to try to decrease the high level of antigen exposure to the fetal brain during that differentiation time.

Question is, is it effective? Perhaps it is quite effective. But the problem is it's administered blindly usually or it's initiated blindly before the ninth week of gestation, until you have the results of a fetal karyotype, and a CAH status is determined. So you end up exposing a lot of pregnancies unnecessarily. You expose the mother, you expose the fetus to prevent external genitalia. The risk based on the mode of inheritance and a 50/50 chance of having a baby girl or baby boy is about one in eight pregnancies. So the ethical question would be would you want to expose eight pregnancies to dexamethasone in hope to try to prevent genital virilization in only one of them? The benefits are that it's effective in reducing genital virilization and possibly eliminating of the genital surgery in a CAH-affected female and decreasing the androgen levels. But there's maternal side effects, such as exposure to glucocorticoids that may be associated with carbohydrate metabolism, diabetes, insulin resistance, and there's a lot of literature about verbal working memory deficits in these children or these fetuses that were treated with glucocorticoids and negative behavioral cognitive outcomes also.

We do not have a lot of long-term data regarding that safety profile of dexamethasone. So this is considered really experimental therapy, and it is also associated with an invasive procedure unless the male karyotype is found by an early genetic test. But there's unnecessary exposure to seven out of those eight pregnancies.

Dr. Turck:
For those just tuning in, you're listening to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Ahmed Khattab about the Endocrine Society Clinical Practice Guidelines for treating congenital adrenal hyperplasia, or CAH.

So now that we have a better understanding of the treatment recommendations for CAH, Dr. Khattab, I'd like to hear more about how you apply these guidelines into practice.

Dr. Khattab:
So we don't have one size fits all, but we follow the guidelines to try to suppress ACTH-driven hyperandrogenism in these patients. And we try to keep the balance between the high-dose glucocorticoids or the supraphysiological glucocorticoid doses to try to keep the balance between glucocorticoid exposure and hyperandrogenemia effects in these individuals.

Dr. Turck:
And I was wondering if you would paint a little bit more of a picture about how these recommendations help optimize outcomes for patients with CAH?

Dr. Khattab:
Well in children, growing children, growth is a huge concern. Safety of the patient is another concern that's very important. And adult fertility is a concern. And the aim of the treatment is to try to minimize all the effects of hyperandrogenism in these individuals. So we hope to try to achieve a better adult height than that one that's predicted. We monitor using biochemical and radiological testin, such as adrenal androgen biomarkers. We test for those regularly, try to achieve targets that may be a little different, depending on the age. We try to, in growing children, we monitor bone age x-rays or skeletal maturation x-rays. In older male individuals, we monitor for testicular adrenal rest tumors by testicular ultrasounds. And adult patients would generally also require monitoring for bone health using the

utilities such as DEXA scan or bone density scans.

Dr. Turck:
Before we end today, Dr. Khattab, are there any final insights or any other thoughts you'd like to share about CAH and its management?

Dr. Khattab:
Yes. I'd like to mention that disruption of the physiological rhythm, or the physiological circadian rhythm, in individuals treated for CAH, may be associated with fatigue in the short term and diabetes and obesity in the medium to long term. Fortunately, children tend to tolerate the cortisol profile well in the short term, but there's also increased evidence of poor health outcomes in the long term. In adult patients, the quality of life may be impaired as a result of non-physiological administration, but it's also in children with CAH, the quality of life is reported to be reduced. And boys and girls are equally affected, so it's not a simple androgen excess concern. And we also have concerns about working memory performance and children with CAH that may be lower compared to their unaffected relatives.

All this leads us to speculation that the abnormal cortisol profile may adversely affect outcomes certainly cognitive development. And the reasons are definitely multifactorial, but it is possible that the abnormal glucocorticoid profile may contribute to this outcome. So at some point, trying to achieve a more physiological cortisol profiles may be very beneficial in these individuals.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Ahmed Khattab, for joining me to discuss the treatment guidelines for congenital adrenal hyperplasia and how we can incorporate them into our clinical practice. Dr. Khattab, it was great having you on the program.

Dr. Khattab:
Thank you so much for having me.

Announcer:
You've been listening to *Clinician's Roundtable*, and this episode was sponsored by Neurocrine Biosciences Inc. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!