All right,

hello, Rich Auchus from the University of Michigan.

I am going to begin this presentation about

unmet medical needs for classic 21-hydroxylase deficiency.

These are our disclosures.

OK, so

in the normal adrenal cortex there are 3 zones

and each of them has its particular job

to make certain steroid hormones.

So the outermost zona glomerulosa

has no 17-hydroxylase activity,

so it's stereogenic pathway is limited to 11-deoxycorticosterone,

which then under the 3 catalytic activities of aldosterone synthase,

which is here represented as P450 11B2, can synthesize aldosterone.

The zona fasciculata is supposed to make cortisol in human beings

and in higher primates; in rodents it makes corticosterone.

And that's because the human zona fasciculata

has the 17-hydroxylase activity

that then allows production of cortisol.

The zona reticularis has both the 17-hydroxylase and very strong 17,20

lyase activity.

So it can go on from 21 carbon steroids to 19

carbon steroids, which are the precursors of androgens.

In particular, the adrenal zona reticularis

makes a lot of DHEA that it sulphates primarily to DHEA sulphate.

The most abundant steroid in the circulation throughout most of life

for most people.

A little bit of the DHEA is normally converted to androstenedione

and very little to testosterone, but as we'll see shortly

when things go awry more than the little bit can come out.

So wait a second gotta get back to my

clicker, there we go.

You have to refresh for a second.

So my phone falls asleep, and then I lose my clicker.

Here we go.

All right, OK so, in 21-hydroxylase deficiency

and we're going to talk,

limit our discussion to 21-hydroxylase deficiency today.

So if we say CAH, we basically mean 21-hydroxylase deficiency,

and in particular we're going to focus on classic disease today.

We'll mention non-classic in a few places

but we're going to really focus on classic disease.

So there is a severe defect of this enzyme, P450 21A2

which, as you notice, is on the pathway

to aldosterone and cortisol.

Now normally you make about 1000 times more cortisol than

aldosterone. So, the box here can either give

you normal cortisol production if you can overcome the block,

which is what non-classic disease is,

or you can have reduced cortisol production,

but a little bit of enzyme activity that allows you to make

that aldosterone big and no act and then you can't make either,

What happens just like when you put a dam in the river,

the water builds up.

It's got to go somewhere

and the only pathways left open are our 2 androgens.

And this is why there is androgen excess in 21-hydroxylase deficiency

and I'll drill down more about exactly what they're making in a second.

First, I want to go over the genetics.

OK.

There we go.

The reason that 21-hydroxylase

deficiency is the most common form of CAH

is that it's in a duplicated locus. It's basically in a booby trap

that the CYP21A1P pseudogene

is adjacent to the 21A2 coding gene

and pieces of the pseudogene can be transferred

into the coding gene by a process called gene conversion.

And this actually happens fairly frequently, and that's why worldwide

you find the same mutations in the majority

of patients with 21-hydroxylase deficiency. There are true mutations.

There are private founder effect mutations,

but they are actually the minority in this disease.

And then as I'll show you, you can also have true deletions.

So here's a slide from a recent paper from Debbie Merke and myself,

where we kind of show the locus in gory detail.

You'll notice this blue gene here, the tenascin B gene,

which overlaps the CYP21A2 coding gene.

So you can have the gene conversion effects

that can

plop in a piece of the pseudogene or you can have true crossing overs,

2 deletions that lop out,

either some or all of the 21-hydroxylase deficiency allele.

So in this case there's a hybrid gene.

In this case the entire 21-hydroxylase gene has been deleted in parts

of the tenascin X gene,

and so the mutations you get can,

are always the same group,

and so we diagnosed this based on basal

and stimulated cortisol and 17-hydroxyprogesterone.

I always, you know

remind people that yes the cortisol should be low

but also the 17-hydroxyprogesterone has to be high

and even better as 21-deoxycortisol. Iâ▯▯ll show you that in a second.

But just in general,

the non-classic disease has maybe slightly reduced but clinically

insignificant reductions in cortisol production

and in elevated 17-hydroxyprogesterone in the thousands.

With the classic disease you have

clinical cortisol deficiency less than 5 micrograms

per deciliter, usually even lower than that,

and then the 17-hydroxyprogesterone is usually at least 10,000,

oftentimes much higher than that.

And I just, the nosology about salt-wasting and simple virilizing,

it's really a clinical diagnosis,

but genetically it usually means that the babies

whose salt-wastes spontaneously

have basically no enzyme activity, and Kiki will discuss this more.

Genetic testing is available, but you know, it's pretty difficult

because of the pseudogene and

you have to count along the chromosome.

You can have 1 copy, 2 copies, 3 copies, 4 copies.

It's not that easy, and oftentimes you need the parents DNA.

So in general, we rely on biochemical testing for the diagnosis.

Now I mentioned the tenascin B gene,
one thing that you might have noticed in
some of your patients
who have deletions is that they have very flexible joints
and this is because the tenascin X
encodes an extracellular matrix protein
and I have a number of patients
who in the top center can put their ankles behind their neck
very easily and do other sorts of things like that, and that's because
the lack, the hemizygous you know
loss of 1 allele of tenascin X can cause this hyper
mobility syndrome and if they lose both copies they have a true
Ehlers Danlos syndrome.
They can have cardiac valve defects and severe connective
tissue problems.
But this is something I've started to look for in my patients.
We call it the CAH-X syndrome.
OK. Here we go. Now, let's.
Let me go back.
All right,
so most patients,
at least in the United States and in many developed countries.
There's this delay. There we go, are diagnosed
based on newborn screening and we measure 17-hydroxyprogesterone
in newborn screen on the blood spot, but...
...there's false positives and false negatives.
If you're not sure,
the diagnosis is made on an ACTH
stimulated panel, usually one of the CH panels

that one of the commercial labs like Quest or ARUP or
or LabCorp provides to both diagnose CAH.
In other words, that cortisol is deficient and precursors are high.
But also sometimes the 17OHP is a little bit high
and actually winds up being another form of
CAH like 11-hydroxylase deficiency or 3 beta-HSD deficiency.
So this is what's done after
the positive newborn screen or an equivocal newborn screen.
So, a
significant fraction of kids are missed on the newborn screen.
Usually this is maternal glucocorticoid administration
and even more concerning is there's a high false positive rate,
and that's because primarily that premature babies have elevated 170HP
And stress causes a rise in 17OHP in infants.
So age adjusted or gestational age adjusted,
17OHPs are more useful and another key is timing.
So what many states do, in fact Texas, that was the first large state
to do statewide newborn screening, recommends
doing a second test for initial positives about a week later.
So either a second screen or an ACTH
stimulation test by a pediatric endocrinologist, but the false,
but all the positive screens have to be followed up.
Other
regions do second tier screening by mass
spectrometry on the blood spots, that takes a few days to get back.
Can I help you?
Can I complain this rate?
So what I would like to say

is that we have a lot of false positives and also false
negative in CAH and that timing, besides all of us,
you know you can have the most sensitive steroid assay by timing.
It's very important and I think it's for
I would like everyone to keep in mind that it's important
to know that the negative CAH clinic result does not rule out CAH
because the HPA axis is highly dynamic
and the 17OHP levels reflect the activity of the HPA axis
only at the time the dry blood spot is collected.
It can be translated
high or translate below. So the 70 node speed levels can be low
even in an affected infant due to the separation of the foetal HPA
activity in utero, which can be caused either
by increased sensitivity of the foetal HPA axis maternal cortisol,
or by increased maternal cortisol
levels levels in foetal circulation due to decreasing activation
of maternal cortisol body, placental enzyme
11 beta-hydroxysteroid dehydrogenase type 2.
Similarly high 170HP levels leading to false positive results
can be seen in a stressed newborn or a premature
baby due to immaturity of the adrenal glands.
The point is that the results of steroid acids
may not accurately represent
the presence or absence of serious disease in the newborn,
but rather represent HPA axis status
at the time the dry blood spots sample was collected,
and in the future incorporation of molecular testing protocols
in the newborn screening of CAH may further improve sensitivity
as molecular testing is not time dependent.

And then it goes back to your reads.
No, no OK. So again, you know, even if so, if the baby passes
the newborn screen, but has clinical adrenal insufficiency,
a female infant with virtualization needs to be evaluated further
and you know
no test is perfect and you know newborn screening for 17OHP
is fraught with difficulties. OK, all right.
So now let's return back to 21-hydroxylase deficiency.
This is the slide I showed you before. Always androgen excess
variable glucocorticoid and mineralocorticoid, and one other point
I want to make as we start talking about the management
of this condition and the testing is that
when things pile up,
OK, and you have high concentrations of precursors
then sort of weird things can happen
and you can get off target metabolism that you don't normally see.
So, for example, you might think that this enzyme here
P450 11B1 which is the adrenal 11-hydroxylase
sitting around twiddling its thumbs with nothing to do
because there is no 11-deoxycortisol being produced.
Instead, what it does
is in the situation where there's a mid 17-hydroxyprogesterone
it just works on that steroid and it makes 21-deoxycortisol.
Now 21-deoxycortisol is usually low
or very low or undetectable in most people,
unless you have 21-hydroxylase deficiency
and this is a specific marker of the adrenal process,
because 17-hydroxyprogesterone is also produced by the gonad,

and the gonad does not have 11-hydroxylase.
So these 11 hydroxylated steroids are very specific for the adrenal
and so some countries and some states
do 21-deoxycortisol for second tier screening
in the face of in elevated or equivocal
17-hydroxyprogesterone because of its greater specificity.
So, what else can 11-hydroxylase do?
Well, 11-hydroxylase can metabolize androgens and did you know
a fish make 11-ketotestosterone as their main androgen?
So, what?
You know it turns out the fish gonad has 11-hydroxylase activity
and the fish testis
converts testosterone to 11-hydroxytestosterone
which is then oxidized to 11-ketotestosterone
this is the major androgen in the bony
fishes, the teleost fish. 11-ketotestosterone is pretty much
as potent as testosterone at the human androgen receptor,
and so if you have an adrenal gland
that's making a lot of androstenedione
as in 21-hydroxylase deficiency and there's 11-hydroxylase present,
you can actually still convert that from androstenedione
using the 11-hydroxylase to 11-hydroxyandrostenedione and
then on to 11-ketotestosterone which again is,
my clicker will work.
Come on, there we go.
Is this steroid here, so and it turns out that 11-ketotestosterone
is actually a major androgen in 21-hydroxylase deficiency
because of its adrenal origin and it's specific
for adrenal androgen access and

other abnormal steroids are for example pregnenolone sulphate.
We usually don't measure that, but it's very high, it's over 10 times
elevated in patients with 21-hydroxylase deficiency.
So this is showing you that now, in addition to the classic pathways,
we have some non-classic steroids that can be very useful for gauging
not just diagnosis but also for disease management.
All right, so.
What do what do we measure?
Well,
first, you want to look at
breaking this up into mineralocorticoids and glucocorticoids.
So to titrate the mineralocorticoids plasma renin,
potassium and in adults, standing blood pressure,
are the three things that I monitor
and I think that this is one of the main mistakes
that endocrinologists
make in taking care of all forms of adrenal insufficiency is not paying
enough attention to the mineralocorticoid replacement.
It's very variable how much people need, we say .1 milligram
a day of fludrocortisone
but I have some people take a milligram a day and others that take .6.
It's just that they're very resistant.
I don't really understand why it is, but they just need a lot.
And then the other steroids
are mainly to look at the glucocorticoid replacement
because realize that right now we use glucocorticoids
not just to replace the cortisol deficiency but
we're also using this to act on the pituitary and hypothalamus

to suppress the HPA axis
and lower the production of adrenal derived androgens.
And so our sort of, you know, the pediatricians,
and again, Kiki will show you a lot more data on this.
They use 17-hydroxyprogesterone a lot.
It's a very sensitive marker.
In adults who are fully grown,
we tend to not use that for monitoring just for diagnosis primarily
for non-classic disease,
we focus more on the androstenedione and testosterone.
When the androstenedione is high,
the patient is not in good control and that's I think a fair statement.
And of course, the androstenedione itself is not the active
steroid, it's the testosterone.
In classic patients,
the only thing the DHEAS tells you is that they're taking their medicine.
It's usually not elevated, and this was one of the bizarre
things that I was trying to emphasize
on the previous slide is because of the rerouting of the steroids.
You would think that in classic 21-hydroxylase deficiency,
DHEAS would be very high,
but it's not, and it's because of these other steroids
that are being produced instead because of the new pathways.
Sex hormone binding globulin is good to get once
so you can calculate free testosterone, but again for monitoring,
you know on a on a routine basis, androstenedione
and testosterone are the main things I do in men and women.
Now, in men I also monitored their gonadotropins.
So, for example,

the testosterone can be in the normal male range,
but how do you know where it's coming from, right?
If it's coming from the testes,
then the testosterone should be higher than the androstenedione,
and the gonadotropins should be normal.
If it's coming from the adrenal,
the androstenedione will be higher than the testosterone
and the gonadotropins will be suppressed, all right.
Fertility semen analysis is the gold standard, if you can get it.
Usually don't do this
until people are actually thinking about starting a family,
but in the meantime,
having the testosterone
higher than the androstenedione and measurable gonadotropins
is a good measure that the control is adequate
enough to allow normal testicular function.
In women, I'm going to mention again
that if they're trying to get pregnant or if they have amenorrhea,
that it's key to follow the follicular phase
progesterone, that's the most important parameter
because progesterone accumulates behind 17-hydroxyprogesterone
and not only impairs ovulation but also thins out
the endometrial lining, prevents implantation, and impairs menses.
So that's the main thing for women who are trying to get pregnant,
trying to conceive, or who are having oligo menorrhea.
OK.
There we go.
The other reason that I point out 11-ketotestosterone is that

if you look at the ratio of the two, in women
it generally correlates linearly because when when they're in poor control
they're making both testosterone and 11-ketotestosterone.
In men it correlates inversely.
So this man is in very good control.
He's not making much 11-ketotestosterone from his adrenals
and all this testosterone is coming from his testes
whereas this man is making a ton of 11-ketotestosterone pretty much
all of that testosterone is coming from his adrenals.
All right, so it's actually a nice, as the androstenedione
testosterone ratio, it's a nice parameter to use for men
with 21-hydroxylase deficiency.
OK, so I'm going to turn it over to Dr. Sarafoglou
now to talk about children with 21-hydroxylase deficiency.
Hello, so in children, response
to hydrocortisone therapy
and this is control is traditionally evaluated
by single measurements of semantic hydroxyprogesterone.
And our androstenedione in clinic visits every 3 to 6 months,
along with clinical impressions, including growth velocity,
weight gain, blood pressure, and cubeta development.
Bone age is typically measured every 6 months as bone
maturation rate reflects the cumulative exposure of bones to androgen
and throughout maturation, accumulative exposure to oestrogen.
Like hemoglobin A1C diabetes,
bone age provides a fuller picture of assessing chronic control of CAH.
The single measurements of adrenal steroids,
collected 3 to 4 times a year, similar to bone age,
clinical signs and symptoms such as changes in growth velocity,

pubic hair development,
technical realisation, blood pressure, and weight measures
represent chronic cumulative exposure to alternating states
of hypo and hypercortisolemia and androgen excess.
You will notice that I listed cortisol in ACPH,
although they are not study about markets using monitoring CAH.
I use them because they provide insights to the status of the HPA
axis following a dose and they can also help assess compliance,
especially in other lessons who stressed those prior to the visit
or when they are adamant that they are religiously compliant,
whenever I suspect that they are not.
The challenges of monitoring disease control is highlighted
in this figure as it shows the wide variability of,
Hold on a second. Did I need to change my slide?
I'm sorry.
I did.
Sorry.
The challenge of monitoring disease control is highlighted
in this figure,
as it shows the wide viability of adrenal steroid biomarkers
even within a 2-hour time frame
in a patient that underwent a 6-hour PKPD study
following the patients, usually in morning hydrocortisone dose.
As you can see in the shaded areas, cortisol
17OHP and androstenedione each had created a 75% change
from the beginning to the end of the 2-hour time frame.
This is why our add-on single runtime measurement
may not provide the most accurate picture of a child's disease control.

For a more accurate picture, it's recommended to document
the time of the adrenal biomarker measurements
relative to the last steroid dose across clinic visits.
Sometimes after changing adults, if I want to get an idea
of the HPA axis response to a new hydrocortisone regiment,
I recommend a follow-up lab visit to measure 17OHP
and Delta 4A at 3 to 4 hours post-dose.
If what I want to determine is maximal suppression response,
or if I want to gauge
a patient's length of adrenal androgen response to a
hydrocortisone dose,
measurement of 17OHP and Beta 4A for concentrations
maybe taken at 6 hours post-dose
when most patientâ□□s adrenal androgens rebound to the pre-dose level
due to hydrocortisoneâ□□s half-life.
I don't know why I have problems with this.
For the CAH guidelines,
the recommended hydrocortisone treatment
is 10 to 50 milligrams
per meter squared per day, dividing into 3 doses.
Babies identified with classic CAH
by newborn screening are treated with fludrocortisone regardless
of salt-wasting status, in order to prevent salt-wasting crisis.
So now recommended by the CAH guidelines
for molecular testing in all infants diagnosed with CAH,
including parental studies, to determine phasing.
A child having a genotype consistent with simple realising form
can be a guide to discontinue fludrocortisone
after the first year of life.

Of course this is done with close electrolyte monitoring.
A plasma renin activity as sometimes children would stenotype,
consistent with symbolizing CAH can still have salt-wasting.
As for long active glucocorticoids
they are not recommended in children because of the negative
effect on growth.
OK.
Except for some incremental adjustments, treatment
for CAH has not had significant advancements in 60 years.
Physicians still struggle to find the right treatment balance
to avoid undertreatment, which leads to excess androgen production
and overtreatment, which leads to glucocorticoids
excess and over suppression of the HPA axis.
Because of the limitations of the current therapy,
children have fluctuating cortisol levels and others in excess every day.
Why is optimal treatment so hard to achieve?
Current therapy does not closely replicate
the falsified secretion pattern of endogenous cortisol.
After that, there is this wide inter-individual
variability of cortisol PKPD parameters
and further as we have all experienced in our practice
simply keeping doses
within the recommended rates does not always prevent adverse
clinical outcomes.
Adding to the challenges of treatment
is hydrocortisone's short half-life,
which is even shorter in children with CAH than individuals
with other forms of primary adrenal insufficiency. This may be due

to the intermittently increase at renal sex steroid production
throughout the day, which could alter enzyme activity of 11
beta-hydroxysteroid dehydrogenase enzymes
and possible other enzymes that have a role in cortisol metabolism.
In this figure,
you can see the treatment with 3 doses of hydrocortisone
can cause supraphysiological spikes in cortisol concentrations
quickly followed by rapid elimination
with hyper cortisol linear between doses.
Most importantly, the evening hydrocortisone
dose was this out in the early morning hours,
resulting in unopposed acetate stimulated
adrenal androgen production.
In our PKPD study of 34 patients with CAH, cortisone returned
very close to pre-hydrocortisone levels by 6 hours
and 17OHP new concentration levels
rebounded to pre-dose levels also within 6 hours.
I point this out because it's a widely held belief that
the biological effect of hydrocortisone can last for 8 hours,
which is not the case
unless the patient has a very prolonged hydrocortisone half-life
As you can see in these panels, there is significant
individual differences
of cortisol pharmacokinetics
and pharmacodynamic response to hydrocortisone dose
among the 34 patients.
In addition to
inter-individual differences, we also have to consider that
intraindividual differences or cure over time,

such as during puberty, where an increase in growth hormone
and ITF 1 levels in can increase cortisol clearance.
Also,
since the primary side of cortisol metabolism in humans is the liver,
obesity, insulin resistance, and fatty liver
cannot record pharmacokinetics and increase the metabolic clearance
of cortisol.
As can be seen in this figure,
the magnitude and the time over 24 hours
that 17OHP and Delta 4A concentrations remain
above or below a target dress code in
a child with CAH underscores that the three dose
hydroculture regimen inevitably leads to periods of hypercortisolemia
and hypocortisolemia and others in excess.
One way to avoid the unopposed rise of ACTH
stimulate adrenal androgen production in the early morning hours
would be to administer hydrocortisone around
3:00 AM when most of the evening hydrocortisone dose,
which is typically administered around 8:00 to 10:00 PM in children
with CAH, has already wash out.
This is of course it's not feasible for most families.
OK.
Will giving hydrocortisone 4 times a day solve the problem?
Unfortunately no.
Photos or PKPD studies have shown that 5/4 times a day
dosing can provide better adrenal biomarker profiles than 3 times a day.
Children will still experience courses of fluctuations and androgen excess.
Another chance of treatment

that is often overlooked
is that normal cortisol secretion is not continuous,
but rather pulsar died following both circadian and ultradian rhythms.
The other panel of the figure shows that ultradian rhythm
in healthy controls consists of approximately
12 cortisol pulses of iron tablet repeated over 24 hours.
And in the lower panel,
you can see how circadian rhythm is actually derived from the
ultradian pattern of cortisol secretion.
Now, why is positive versatility important?
Possible access of glucocorticoids to the receptors
have been shown in vitro
and in vivo in animal models to be of critical importance
for gene regulation, non-genomic glucocorticoid
signaling, HPA axis regulation and endocrine
and neuro behavioral responses.
The one change that
there has been in CAH therapy over the past 50 years
is that the recommended total daily hydrocortisone dose has decreased.
While this is a positive change,
long-term outcomes are still not optimal.
In our longitudinal study of 104 children with CAH,
each one milligram per meter squared per day of hydrocortisone dose
increase lead to a decrease of .37
centimeters of estimated adult height.
What we also found is that children with hydrocortisone doses
within the recommended range of 10 to 15 milligrams per
meter squared per day
still had sold stature, suggesting that other factors

besides total daily hydrocortisone doses may play a role.
Daily dose distribution and timing as well as individual
cortisol PKPD parameters. As some of the other factors that could
determine the patients exposure to hyper and hypocortisolemia.
In another study,
we found that children with CAH have increased hypertension rates.
While no relationship was found between hydrocortisone dose
and hypertension, there was, however
a significant correlation between over suppression
score and hypertension, which again highlights that we need to move
towards more personalized treatment that focus on individual response
to hydrocortisone,
rather than simply looking into those
within recommending rates who can still lead to over suppression,
as some individuals are more corticoid sensitive than others.
In a case that highlights
most of what we have been discussing is that of a 7-year-old female
diagnosed with salt-wasting CAH who came to see me
for a fourth opinion. She presented with cushingoid features,
growth deceleration, hypertension, and weight gain,
and at presentation her androstenedione, ACTH and cortisol
were undetectable and her 17OHP was 40 nanograms
per TL 12 hours, post her evening dose.
Interviewing her medication history,
she was treated with multiple hydrocortisone formulations and viable
total daily hydrocortisone dosing, most within the recommended range,
and treatment decisions were focused on normalizing adrenal androgens.
At presentation, she was receiving 8 milligrams per meter squared per day

given in reverse circadian fashion with the goal of suppressing
adrenal androgens during the early morning hours.
A case that highlights,
so this patient underwent a 6 hours cortisol PK study
with cortisol clearance and volume of distribution
where in the lower quartiles,
resulting in a half-life in the average range.
The fact that she was she was not a slow metabolizer
and she has be treated with doses mostly in the recommended range,
suggesting that sheâ□□s glucocorticoid sensitive
which contribute to over suppression of cushingoid features,
Yet another daily hydrocortisone dose was changed to 6 milligrams
per meter squared per day, which is below the recommended
range, and was administering in a circadian pattern.
In one year follow-up as the photos indicate her symptoms got resolved
along with recovery of HPA and growth access
and now I will turn back to Dr. Auchus.
Rich?
Yes, it said to unmute.
OK, now I gotta get back on my clicker.
All right, so,
So in adults, you know when I got involved with this field,
all the review articles said when they're adults
you switch them to a long acting glucocorticoid.
I don't do that.
I actually try to leave them on hydrocortisone.
Because it is least likely to
cause long-term problems and I'll show you some evidence for that
in the future.

So if they're doing
well on hydrocortisone, I leave them on hydrocortisone.
The problem is, as people you know, get into adulthood
and they have jobs and they go to school and you know it
sometimes becomes difficult for them to take 3 doses a day.
But I'll tell you if they're just a little bit out of control,
and I also say that I think nothing replaces the cortisol deficiency
as well as hydrocortisone because of the nice rise
that you get in the morning, so if they're adequately replaced,
but yet their androgens are too high, then
a small bedtime dose of a long acting glucocorticoid
is often sufficient to get the androgens under control.
And so I'm talking like a milligram of
prednisolone or 2 milligrams of methylprednisolone.
If you give dexamethasone or prednisolone, you usually have to give it
as the liquid, not as the tablets
because you can't titrate the dose small enough.
Methylprednisolone comes in 4 milligram tablets,
so a half of a 4 milligram tablet you can get away with.
If they just need to take
something twice a day, then prednisolone or methylprednisolone.
I don't like to use prednisone itself because it is a prodrug
and it's very unreliable and I stick to circadian rhythm.
So in other words, the morning dose replaces the cortisol deficiency.
And then the minimum bedtime dose to control the androgen
excess, not reverse circadian dosing.
And dexamethasone, I really reserve for specific situations
like the one I'll mention

in a second with men.

So how are we doing in adults? Well, not so well.

There have been two large studies, one from the UK,

the Chase study, and one from the NIH from Debbie Merkeâ□□s group.

So if you look broadly

at these patients, higher suppressed androgens are common.

Many of them are obese with metabolic

syndrome and insulin resistance. There's hypertension

that's even more common in the classics than in the non-classics,

even though they were hypotensive as children.

Low bone density is common,

and you know these are young adults.

I mean, these studies,

most of these people are in their 20s and 30s.

So when you see 37% have low bone density, that's not a good thing.

And adrenal rest tumors in a large number of boys and men,

I'll show you that in just a second, and the dosing is all over the place.

People are on all kinds of things. And the non-classic

are getting even more dexamethasone than the classics,

which doesn't make any sense. So we don't really have a standard

and we don't really have a good approach to these patients right now.

Specific problems with men and women, men,

in addition to the hypothalamic pituitary adrenal axis,

which is trying to make cortisol but in the patient

with 21-hydroxylase deficiency can only make androgens,

they have the hypothalamic pituitary gonadal axis

and, as I mentioned before, the pituitary doesn't know

where the androgens are coming. So if the adrenal androgens are high,

the gonadotropins will be suppressed and without intra testicular

testosterone production
there will be poor sperm production and infertility.
The other main reason for infertility,
is these testicular adrenal rest tumors
which we used to think were miss migrated adrenal cells,
but they're actually probably reprogrammed lighting stem cells.
They tend to be firm,
irregular, bilateral masses that start in the rate a testes
and I've shown you a couple of ultrasound
images of a normal testis, small
adrenal rest tumors that you wouldn't be able to palpate,
and then a testis that's been completely replaced
by adrenal rest tumors.
That's the second main cause of infertility.
Another tumor that is well
and adrenal rest tumors can actually develop in women as well.
We just don't pick them up
because we can't palpate the ovaries as easily, and this is in an image
of adrenal rest tumors in a woman who had undergone
a bilateral adrenalectomy for CAH when her androgen excess came back
a couple of years later.
This is a reason why we don't recommend bilateral adrenalectomy.
It doesn't really fix the problem in men or women long-term.
Another tumor that's characteristic of CAH patients are massive
adrenal myelolipomas.
If you see someone with bilateral large
myelolipomas, this is typical of 21-hydroxylase deficiency.
They're not cancerous, but they just tend to keep growing.

The largest one I've seen is 30 centimeters.
This one is about 18 centimeters.
But this is one reason why people can sometimes have to have
their adrenals removed because they eventually cause mass effects.
I'm going to finish with a quick case about a young woman.
As I mentioned before,
high androgens are a problem, but actually for infertility,
high adrenal derived progesterone is the main problem.
In addition, not that many women with classic disease even
attempt to get pregnant, in part because
of the general genital virilization,
the need for reconstructive surgery to have vaginal intercourse,
and sometimes the restenosis that occurs.
But this is a woman, who I take care
of now, who did well with hydrocortisone as a child,
and I kept her on the hydrocortisone 10 TID
as a young adult. She also got .2 milligrams day of fludrocortisone.
For a while, she had regular menses but she was on a birth control pill.
And she didn't complain of hirsutism or acne.
And then gradually overtime her control deteriorated,
and I see these in some people. I'm not sure what's happening.
I don't know if it's that they're skipping midday doses.
Sometimes people will admit to that,
I can't remember to take my midday dose,
but her testosterone drifted up her and androstenedione was
definitely high,
but her weight was stable and I didn't change her regimen just for that.
But then, she told me she wanted to have children and so we stopped her
birth control pills. Her menses were erratic.

Her androstenedione was still quite high
and her testosterone was elevated so I knew her progesterone was high
and I added a little bit of prednisolone at bedtime
and her lab started to get into control. I had to raise
the prednisolone dose up to 2 milligrams at bedtime and,
she's still not pregnant after 4 months.
And so this time I measured the follicular phase progesterone
and the goal would be about .6 nanograms per mil
and she was,
even though her androstenedione was normal, her progesterone was high
so I raised her prednisolone dose again to 3 milligrams
at bedtime. And finally, her menses got regular.
But when I examined her
she was clearly cushingoid and even though I got her progesterone down
finally I had to make her cushingoid in order to do it.
So I told her, let's hold the prednisolone for a couple of weeks.
Let's let your body recover from it,
and then we'll try to start over again at a lower dose.
And a couple months later she called me back that she was nauseated,
her periods had stopped, her legs were swelling.
And well, she's pregnant and
she delivered a healthy baby girl.
In fact, she's pregnant again now
and she's about to deliver her second child by C-section next week.
And this, I think illustrates in in adults
the problem that we can get them under control
and we can get them to be fertile with the current regimens.
But we can't do this long-term

because of the limitations of the high dose glucocorticoids.