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1. Introduction

Among the most common causes of female infertility, anovulation, menstrual irregularity, hirsutism, acne, and alopecia are congenital adrenal hyperplasia (CAH) and polycystic ovarian syndrome (PCOS). These two conditions resemble one another quite a bit, especially the non-classic forms of CAH (NCAH). Another common cause of such problems is hyperprolactinemia, which results in increased androgen synthesis by both the ovaries and the adrenal cortex, while suppressing gonadotrophin-releasing hormone, gonadotrophin, and estrogen synthesis. Hyperprolactinemia, in turn, may be caused by primary hypothyroidism, prolactinomas, stalk effects of other pituitary and hypothalamic neoplasia, as well as a host of prescription and recreational drugs; it may also be idiopathic. Other, less frequently encountered causes of these problems include Cushing’s syndrome and virilizing tumors (ovarian, adrenal, or ectopic). A growing worldwide problem in this sphere is androgen doping to improve athletic performance.

Additional causes of menstrual irregularity include uterine leiomyomata, puberty, perimenopause, chronic illnesses eg. poorly controlled diabetes mellitus and sickle cell disease, elite athletics and dancing, eating disorders, endometriosis, and Asherman’s syndrome.

Infertility may also be caused by stress, tubal factors, Asherman’s syndrome, immune response to spermatozoa, luteal phase inadequacy, and male factors.

In this chapter we shall focus on 3 novel concepts:

• The treatment of the congenital adrenal hyperplasias and the acquired/unmasked adrenal hyperplasias by interventions which reduce insulin resistance.
• The induction of PCOS and enhanced 1-α-hydroxylation of 25-OH-vitamin D by parasite endocrine disruption.

• The amelioration of the latter by alteration of the hormonal milieu.

2. Insulin resistance in CAH

2.1. Recognition of insulin resistance in CAH

The first report of insulin resistance in CAH was published by Speiser et al. in female patients with non-classic 21-hydroxylase deficiency [1].

In 1994 Andersson et al. reported that women with type 2 Diabetes Mellitus (T2DM), the archetypal insulin-resistant condition, had higher mean free testosterone levels, higher waist/hip ratios, lower sex hormone-binding globulin (SHBG) levels, and higher plasma insulin levels than gender/BMI matched controls [2]. In commenting on the report of Andersson et al., Sacerdote reported a sample of 57 consecutive male and female T2DMs, all of whom had adrenal hyperandrogenism [3].

In 2005 Saygili et al. reported that women with non-classic 21-hydroxylase deficiency were both insulin and leptin resistant compared BMI-matched controls [4].

Several groups have reported insulin resistance as a common feature of both classic 21-hydroxylase deficiency and classic 11-hydroxylase activity [5-14]. Importantly, in most of these studies, the insulin resistance was independent of the corticosteroid dosage, suggesting that it is intrinsic to CAH, rather than a result of exogenous corticosteroid. Glucocorticoid receptor polymorphism (BcII GR variant) may contribute to the insulin resistance as reported by Moreira et al [14].

In 2006 we reported additional endocrine disrupter effects of two classes of drugs used in anti-retroviral therapy that were already known to cause insulin resistance, protease inhibitors and nucleoside analogues—the induction/unmasking of adrenal hyperplasia [15].

Despite the slowly growing recognition that insulin resistance is an intrinsic feature of both CAH and acquired/unmasked CAH, just as is in PCOS, the medical community has been very slow in exploring treatment approaches based on improving insulin sensitivity analogous to the treatment approaches now used so successfully in PCOS. This is despite the widely recognized limitations of mainstream corticosteroid replacement therapy, which, as excellent as it is, often cannot normalize androgen levels without producing adverse effects of glucocorticoid excess, such as decreased bone mineral density, hyperglycemia, soft-tissue changes, and affective changes. The respective advantages and disadvantages of corticosteroid replacement therapy, including the latest advances are discussed extensively in our earlier chapter [16].
2.2. Treating CAH by reducing insulin resistance

In 2000 we reported the first series of patients with T2DM/pre-diabetes and non-classic CAH (NCAH) in whom the biochemical and clinical features of NCAH were ameliorated by treatment with metformin and/or troglitazone [17], from 2 different classes of insulin sensitizers, biguanides and thiazolidinediones.

In 2003 we reported that the biochemical/phenotypic expression of NCAH, including 21-hydroxylase deficiency, 3-β-ol dehydrogenase deficiency, 11-hydroxylase deficiency, and aldosterone synthase deficiency could be ameliorated with the thiazolidinedione insulin sensitizer, rosiglitazone [18]. An example of this is shown in Figure 1. Of note, in this patient, the observed sharp drop in serum 17-OH-progesterone occurred within 24 hours of initiating rosiglitazone, consistent with an effect on DNA transcription/ mRNA translation.

Figure 1. Response of a 43 year old male’s 17-OH-Progesterone (ng/dl) to rosiglitazone 4mg bid.

In 2004 we reported that the biochemical/phenotypic expression of NCAH is ameliorated by pioglitazone [19]. An example of the combined effect of metformin and pioglitazone compared with standard glucocorticoid/mineralocorticoid replacement therapy in a patient with non-classical 21-hydroxylase deficiency is shown in Figure 2. Note that the response of the patient’s serum 17-OH-progesterone to the insulin sensitizers, metformin and pioglitazone is more complete than to the standard of care therapy with glucocorticoid and mineralocorticoid.

Figure 2. Response of a 57 year old female’s 17-OH-Progesterone (ng/dl) to cortisone acetate, metformin, & pioglitazone
Arslanian et al. reported that metformin therapy in obese teen-agers with PCOS and impaired glucose tolerance (IGT) attenuated the exaggerated adrenocortical response to ACTH with a reduction in hyperinsulinemia/insulin resistance [20].

In 2007 we reported that the anti-psychotic drugs and valproate, which were already known to cause insulin resistance and, in the case of the latter, PCOS, also induced and/or unmasked adrenal hyperplasia [21]. This endocrine disrupter effect of these drugs was reversible with the insulin sensitizers metformin (Figure 3) or rosiglitazone (Figure 4).

![Figure 3. Effect of metformin on elevated steroid metabolites in 8 patients (represented as % of baseline)](image1)

![Figure 4. Effect of rosiglitazone on elevated baseline 11-Deoxycortisol level (mg/dl) in 2 patients](image2)

17 OH Preg = 17-OH-pregnenolone
17-OH Progest = 17-OH-progesterone
DOC = deoxycorticosterone
11 DOC = 11-deoxycortisol
E1 = estrone, E2 = estradiol
In 2008 we published the first report of a patient with classical, salt losing 21-hydroxylase deficiency being successfully treated with the addition of metformin to standard corticosteroid therapy (Figures 5,6) [22]. The patient was a 17 year old woman, whose CAH had been diagnosed in the nursery, where she had become profoundly dehydrated, whose current complaints were of amenorrhea, hirsutism, and acne, despite being adherent to optimal glucocorticoid/mineralocorticoid therapy. As can be seen in figure 5, her baseline serum 17-OH-progesterone on standard therapy was still very elevated, while her baseline serum total testosterone (Figure 6) was actually in the lower reference range for adult males. While maintaining this therapy, metformin 500 mg twice daily after meals was added. Co-incident with the marked reduction in both her serum 17-OH-progesterone and serum testosterone levels documented at her next visit, she noted the return of monthly menses, the absence of new acne lesions, and a reduction in hirsutism. While we would have liked to continue to titrate her metformin dose upward to 2 grams daily and, if necessary, added a second insulin-sensitizing agent in an attempt to normalize her steroid metabolite levels, and then possibly, wean her off corticosteroids altogether, the patient pronounced herself pleased with the results shown here and declined further dose titration and/or addition of other insulin sensitizers.

**Figure 5.** Effect of metformin on 17-OH-progesterone (ng/dl) in a patient with classical, salt-wasting 21-Hydroxylase deficiency

**Figure 6.** Effect of metformin on serum total testosterone (ng/dl) in classical, salt-wasting 21-Hydroxylase deficiency
Before proceeding to discuss other insulin-sensitizing options in the treatment of CAH and endocrine-disrupter induced/unmasked adrenal hyperplasia, it is worth discussing a few limitations to their use. Despite their demonstrated efficacy, these insulin sensitizers have still not been demonstrated to be able to totally replace corticosteroids in classical CAH nor have they been prescribed, to our knowledge, in forms of CAH such as lipid CAH.

The main limitation of metformin use is gastrointestinal intolerance. Much of this problem may be overcome by prescribing more gastrointestinal-friendly forms of metformin such as extended release, liquid (Riomet), or matrix-embedded (Glumetza). Unfortunately, the latter two forms, which are exceptionally well-tolerated, are often not covered by prescription insurance.

Another significant limitation of metformin use is that is inappropriate to use in patients with seriously compromised renal function due to an increased risk of lactic acidosis. In the U.S. it is recommended that metformin not be used in women with serum creatinine >1.4 mg/dl or men with serum creatinine > 1.5 mg/dl. In several other countries guidelines are allowing its use at lower doses down to an eGFR > 35 ml/min.

The use of thiazolidinediones is limited because there is little experience with this class of drugs in mid-late pregnancy and there is concern about weight gain, bone loss, and bladder cancer.

Another means of improving insulin sensitivity is with diet and exercise. This approach was utilized in 2 patients with non-classic aldosterone synthase deficiency (Figure 7) [23]. Diet and exercise resulted in a 10% weight reduction accompanied by a normalization of the elevated serum deoxycorticosterone levels and normalization of the elevated LH/FSH ratio and improvement in the clinical features of virilization.

Figure 7. Changes with weight loss & exercise in 2 women with non-classic aldosterone synthase deficiency

Metabolic or bariatric surgery in obese T2DM patients has been associated with an improvement in insulin sensitivity associated with weight loss, suppression of inappropriate glucagon secretion via observed increases in GLP-1, reductions in glucose toxicity via improved glycemic control, and increased glucose utilization associated with intestinal villous hypertrophy/hyperplasia distal to the anastomotic site. It is also reported to ameliorate PCOS [24].
We reported the first patient in whom Roux-en Y gastric bypass not only caused the patient’s T2DM and hypertension to remit, but also normalized the biochemical and clinical expression of her non-classical 11-hydroxylase deficiency (Figure 8) [25].

Ashwagandha root (Withania somnifera) has been used for millennia in Ayurvedic medicine, where it has proven effective in treating a number of specific conditions as well as being used as a general “tonic”. We recently reported a patient who complained of excessive scalp hair shedding who was investigated and found to have both non-classic 3-β-ol-dehydrogenase deficiency and aldosterone synthase deficiency with elevated baseline levels of both serum 17-OH-pregnenolone and corticosterone [26]. The patient had been able to reduce her rate of scalp hair loss and normalized her serum levels of both steroid metabolites while taking pioglitazone 15 mg/day. The patient elected to, nevertheless, stop pioglitazone because of what she had read on the internet concerning osteoporosis and bladder carcinoma. She promptly started losing excessive scalp hair again. After watching the Dr. Oz television program she decided to start a standardized preparation of Ashwagandha root 400 mg twice daily as a general “tonic” and anti-oxidant. At her next visit she reported that she was awakening in the morning with much less hair on her pillow. Repeat serum levels of 17-OH-pregnenolone and corticosterone again fell to normal while using Ashwagandha root (Figures 9,10). A report by Anwer et al. confirms that Ashwagandha, among other effects, is an insulin sensitizer [27].
Metformin treatment was not initially an option in this patient as he had a life-threatening lower extremity infection with gangrene. Metformin would have increased his risk for developing dangerous lactic acidosis. His diabetes was, therefore, treated with basal/bolus insulin. Vitamin D replacement was begun using ergocalciferol 50,000 IU once a week. His serum 11-deoxycortisol fell from a baseline value of 2024 ng/dl (nl<76) to <20 ng/dl over a period of 28 days, while his serum 25-OH-vitamin D$_3$ level rose concomitantly from a baseline value of 12 ng/ml (nl>30) to a level of 27 ng/dl on the 17th day of replacement (Figure 11). The 28 day Vitamin D sample was lost by the laboratory. It is known that the adrenal cortex has Vitamin D receptors (VDR’s) [30]. Thus, Vitamin D may also enhance the expression of adrenal steroidogenic enzymes via cross-talk.

There is now considerable evidence that Vitamin D is an insulin sensitizer [28]. We recently reported a patient with T2DM, classical 11-hydroxylase deficiency, and severe Vitamin D deficiency [29].

Metformin treatment was not initially an option in this patient as he had a life-threatening lower extremity infection with gangrene. Metformin would have increased his risk for developing dangerous lactic acidosis. His diabetes was, therefore, treated with basal/bolus insulin. Vitamin D replacement was begun using ergocalciferol 50,000 IU once a week. His serum 11-deoxycortisol fell from a baseline value of 2024 ng/dl (nl<76) to <20 ng/dl over a period of 28 days, while his serum 25-OH-vitamin D$_3$ level rose concomitantly from a baseline value of 12 ng/ml (nl>30) to a level of 27 ng/dl on the 17th day of replacement (Figure 11). The 28 day Vitamin D sample was lost by the laboratory. It is known that the adrenal cortex has Vitamin D receptors (VDR’s) [30]. Thus, Vitamin D may also enhance the expression of adrenal steroidogenic enzymes via cross-talk.

![Figure 10. Response of patient's serum corticosterone (ng/dl) to Ashwagandha 400 mg Twice Daily](image1)

![Figure 11. Changes in serum 11-deoxycortisol (left) as a function of changes in serum 25-OH-Vitamin D$_3$ (right) at baseline and at 9 days and 17 days after starting ergocalciferol 50,000 IU daily.](image2)
Most recently, we have reported a patient whose non-classic 11-hydroxylase deficiency was improved by taking a combination of Vitamin D and the GLP-1 receptor agonist liraglutide (Figure 12) [31]. GLP-1 receptor agonists improve insulin sensitivity by suppressing the inappropriate secretion of the counter-regulatory hormone, glucagon, decreasing glucose toxicity by lowering post-prandial and fasting glucose levels and over time by weight, (visceral fat mass) reduction.

![Figure 12. Response of Patient’s Serum 11-Deoxycortisol (ng/dl; ref. range <42 ng/dl) to treatment with ergocalciferol & liraglutide](image)

### 2.3. Possible mechanisms by which reducing insulin resistance ameliorates congenital adrenal hyperplasia

Kelly et al. studied the effects of insulin in an in vitro human adrenocortical cell culture [32]. They reported that steroidogenic factor-1 (SF-1) activity is up-regulated in vitro by insulin in the presence of forskolin (a functional analog of ACTH in this setting). Increased SF-1 synthesis, as well as increased binding of SF-1 to its response element, resulted in increased transcription of CYP17 causing increased adrenal androgen synthesis in both normal, human adrenocortical tissue and in cultures of the adrenocortical tumor line H-295. In these same two in vitro systems insulin inhibited the forskolin (ACTH) stimulated synthesis of the transcription factor nur77, an action that results in decreased transcription of CYP21 mRNA, further directing adrenal steroidogenesis toward androgen vs cortisol biosynthesis. Thus, hyperinsulinemia would worsen the phenotypic/biochemical expression of 21-hydroxylase deficiency as well as magnify any other deficiencies of adrenal steroidogenic enzymes.

### 2.4. Future directions in the treatment of congenital adrenal hyperplasia by reducing insulin resistance

A number of drugs, herbs, naturally occurring compounds, as well as other therapeutic interventions have been shown to improve insulin sensitivity. While the efficacy of metformin and the thiazolidinediones in the treatment of NCAH is now established, it is still unknown if these agents could completely replace corticosteroids in classical CAH. Similarly, while we have shown in one patient that Vitamin D replacement can obviate the need for corticosteroids in a patient with classical 11-hydroxylase deficiency, we do not know if Vitamin D would work
as well in other classical forms of CAH or in CAH patients without vitamin D deficiency/insufficiency. Randomized control trials will be needed to answer these important questions.

It is now recognized that dopamine receptor agonists have an in insulin-sensitizing effect [33, 34] and a formulation of the dopamine receptor agonist, bromocriptine, is now used to treat T2DM. Both bromocriptine and cabergoline, another dopamine receptor agonist, have been used to treat PCOS [35,36]. Since most insulin sensitizing treatments that are successful in PCOS turn out to be successful in treating NCAH, a pilot study using these agents in NCAH seems reasonable.

The bile acid binding resin, colesevelam, has been reported to improve insulin sensitivity, possibly by causing an increase in endogenous GLP-1 secretion [37,38]. This finding might be a basis for a pilot study using this agent to treat CAH.

The fat absorption blocking agent orlistat is approved as a weight loss aid when combined with diet and exercise in the U.S. in both a 60 gm over the counter form and a prescription only 120 mg form. In Canada it is approved for the treatment of T2DM. Panidis et al. reported that orlistat in combination with diet produced significant weight loss and improvement in insulin sensitivity in obese women, with or without PCOS [39]. In addition, serum testosterone levels were significantly improved in women with PCOS. Based on these data pilot studies of orlistat in NCAH should be performed. Stimulation of the CB-1 cannabinoid receptor has known orexic and euphoric effects, while its blockade with rimonabant has been associated with anorexic and dysphoric effects and results in weight loss, reduced insulin resistance, and improvements in glycemia and serum lipid levels [40] and has shown efficacy in PCOS patients [41]. Rimonabant was not approved in the U.S. and its approval was withdrawn in Europe because of a higher suicide risk due, presumably, to its dysphoric effect. The risk/benefit ratio of this class of agents might be improved by better patient selection, selective co-administration of an anti-depressant, treatment of hyperhomocysteinemia (which may play a role in depression, or the development of selective cannabinoid receptor modulators, possessing the beneficial anorexic effect of the class without causing dysphoria.

The selective estrogen receptor modulators (SERM’s), now in widespread clinical use, provide a model for such future development. Since CB-1 receptor blockers reduce insulin resistance, we might predict that they could ameliorate CAH.

Many, if not most, insulin resistant people have obstructive sleep apnea (OSA) [42]. Vgontzas et al. have reported that the inflammatory cytokines, TNF-α and IL-6 are elevated in patients with OSA, independently of obesity and that visceral fat was the primary parameter linked with OSA [42] and treatment with CPAP has been shown to improve insulin sensitivity in women with PCOS [43]. The fact that they found that OSA was more common in women with PCOS suggested a pathogenetic role of insulin resistance in OSA. The beneficial effect of a cytokine antagonist on excessive daytime sleepiness in obese, male apneics and on sleep disordered breathing in a general, random sample supports the hypothesis that cytokines and associated insulin resistance are mediators of excessive daytime sleepiness and OSA. Hamada et al have reported that with nasal CPAP in a CAH patient with OSA they were able to reduce the maintenance glucocorticoid dosage [44]. CAH patients, who have clinical features consis-
tent with OSA, might benefit from undergoing a sleep study followed by a CPAP titration study if the initial sleep study is diagnostic. Alternatively, inhibitors of TNF-α and IL-6 might be useful adjuncts in the treatment of CAH.

Curcumin is a component of the popular spice, turmeric. It has been reported to decrease levels of the inflammatory cytokine, TNF-α, which, in turn, downregulates the transcription factor PPAR-γ. Administration of curcumin results in up-regulation of PPAR-γ mRNA and protein, which we would predict would improve insulin sensitivity [45]. Pilot studies with curcumin in CAH patients, would, therefore, be of interest given the absence of any known adverse effects. Other spices, herbs, and supplements known or suspected to have insulin sensitizing effects would also be worth exploring in CAH.

Somatostatin and its analogs-octreotide, octreotide LAR, and lanreotide partially suppress insulin secretion; reduction of hyperinsulinemia by this means could result in amelioration of both PCOS and CAH. Gambineri’s group reported that octreotide-LAR improved the ovulation rate and hirsutism and showed nearly significant trends toward greater reductions in serum testosterone and androstenedione compared with placebo in dieting women with abdominal obesity and PCOS [46]. Pilot studies of these drugs in these two conditions, would, therefore, be of interest; because they reduce the secretion of growth hormone they would not be suitable for use in children or adolescents.

Phenytoin and diazoxide both decrease insulin secretion and have been reported to be helpful in treating some PCOS patients [47,48]. On this basis we might predict a response in CAH patients as well. In designing pilot studies with these agents, patients with pre-diabetes or low bone density should probably be excluded due to the diabetogenic potential of both drugs and the accelerated Vitamin D clearance attributed to the latter.

### 2.5. Summary of treatment of CAH using insulin sensitizing approaches

- Insulin sensitizing approaches, including diet/exercise, metformin, thiazolidinediones, bariatric surgery, Ashwagandha root, Vitamin D replacement, and liraglutide can eliminate the need to use corticosteroids in the treatment of non-classical adrenal hyperplasia and valproate/anti-psychotic induced/unmasked adrenal hyperplasia due to 21-hydroxylase deficiency, 3-β-ol dehydrogenase deficiency, 11-hydroxylase deficiency, and aldosterone synthase deficiency.

- Metformin addition can improve the outcome in classical CAH due to 21-hydroxylase deficiency, exerting a corticosteroid-sparing effect.

- Vitamin D replacement in Vitamin D deficient/insufficient patients with NCAH due to the above enzyme defects can eliminate the need for corticosteroids.

- Vitamin D replacement can replace the use of corticosteroids in classical 11-hydroxylase deficiency associated with vitamin D deficiency.

- It is desirable to eliminate or minimize the use of corticosteroids in CAH in order to avoid adverse drug reactions, including hyperglycemia, bone loss, growth retardation, and affective changes.
• The amelioration of CAH by insulin-sensitizing approaches suggests that, as in PCOS, insulin resistance is an integral part of the pathogenesis of the CAH’s.

3. Parasitic endocrine disruption; polycystic ovarian syndrome induced by neurocysticercosis

3.1. Background

There is growing awareness of the role of environmental endocrine disrupters in human health and reproduction as well as in the health and reproduction of other species. Most of the research in this area has dealt with the menace of manmade endocrine disrupting chemicals (EDC’s), such as phthalates and hydraulic fracking chemicals. We are also rediscovering the endocrine disrupting role of parasites, which have preyed upon our species since prehistoric times. An example of this appears in statues of the pharaoh, Akhnaton which have often portrayed him as a young man with rounded hips and gynecomastia. Some historical epidemiologists have suggested that this feminized appearance might be the result of hepatic involvement by schistosomiasis, which has long been endemic in the Nile Valley.

3.2. PCOS induced by neurocysticercosis

The patient we reported was a 33 year old (at that time) Mexican woman G3P2012 with extensive neurocysticercosis, who was referred to our clinic for secondary oligomenorrhea, acne, and hirsutism [49]. She had no localizing neurologic signs and none of the cestodes directly involved the hypothalamus or the pituitary gland. There was no family history of PCOS. She had previously conceived three times without difficulty, followed by 2 normal pregnancies and 1 elective abortion. Her BMI was 28.34 kg/m² and was almost unchanged from 2003 to 2011. She had not become pregnant again despite having regular relations without contraception. Although her serum free and total testosterone, androstenedione, DHEA, and DHEA-S levels were normal, a diagnosis of PCOS was made by the Rotterdam criteria—the combination of oligomenorrhea plus clinical features of hyperandrogenism and the exclusion of CAH. The diagnosis was further supported by the findings of an elevated LH/FSH ratio and a low concentration of SHBG, which is evidence for both hyperandrogenism and insulin resistance. Although her baseline serum 25-OH-vitamin D₃ level was normal at 34 ng/dl, her serum 1,25-(OH)₂-vitamin D₃ level was elevated at 81 pg/ml. The patient refused standard treatment for cysticercosis with albendazole and dexamethasone because several of her friends had experienced adverse drug reactions with this therapy.

We initiated treatment of her PCOS with a 1200 kcal reducing diet, daily 30 minute walks, and metformin 500 mg twice daily after breakfast and supper. On this treatment monthly menses resumed, but periods lasted for only 2 days each cycle. After the metformin dosage was increased to 850 mg twice daily monthly menses continued and periods now lasted for 4 days. Hirsutism and acne noticeably diminished, however, she still did not conceive despite continuing regular relations without contraception (Table 1).
Table 1. Parameters related to polycystic ovarian syndrome

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Units and reference ranges for the parameters given in the table: BMI, body mass index kg/m² [20–25]; FSH, follicle stimulating hormone mIU/l (1.37–17.20); Insulin mIU/l (<17.0); LH, luteinising hormone IU/l (1.9–76.3); LH/FSH (≤1.0); SHBG, sex hormone binding globulin nmol/l (17–120).

In performing a literature review to ascertain if there could be an association between PCOS and cysticercosis, we learned from publications that the encysted forms of Taenia sp. are virtual steroid factories, producing such metabolites as androstenedione, testosterone, estradiol, and 17-OH-progesterone [50-56].

Morales-Montor et al., in discussing host gender preference in mammalian parasitoses, reporting that Taenia sp. exhibit a marked female host preference, and even more readily infect and reproduce in pregnant hosts. When they do infect a male host, they will feminize the host via estradiol production [55].

Given the host preference of this parasite, it would seem counterintuitive that the Taenia cestodes would produce the hyperandrogenic state of PCOS, until one remembers that PCOS is also a state of unopposed estrogen, characterized by such features as superficial cell predominance on vaginal cytology, cervical mucus ferning on low power microscopy, spinnbarkeit, and withdrawal bleeding after progesterone challenge.

3.3. Treatment of cysticercosis with selective estrogen receptor modulators (SERMs)

Vargas-Villavicencio et al. reported that treatment of mice infected with Taenia crassiceps with the SERM, tamoxifen, resulted in a rapid, dramatic 80% reduction in parasite burden in infected females and a 50% reduction in males [57]. Tamoxifen increased the Th1/Th2 ratio favoring increased expression of cellular immunity as well as being associated with a change in the cytokine pattern consistent with greater Th1 expression. They also reported that cultured Taenia crassiceps cestodes that were exposed in vitro to tamoxifen concentrations comparable with those achieved in human treatment died rapidly.

After again declining standard treatment of her neurocysticercosis with albendazole and dexamethasone, we discussed with our patient the work reported by Vargas-Villavicencio et al. and obtained her fully informed consent to initiate a course of treatment with another SERM, raloxifene 60 mg orally daily. Pregnancy and disorders predisposing to a hypercoagulable state were excluded before commencing treatment. Raloxifene, rather than tamoxifen, was chosen so as not to increase the patient’s risk for endometrial cancer and because the former
is known to exacerbate post-menopausal vasomotor symptoms in early post-menopausal women, suggesting that it readily crosses the blood/brain barrier, acting as an estrogen receptor antagonist within the central nervous system. Raloxifene was added to metformin 850 mg twice daily beginning on January 21, 2010. The patient was reminded of the need for reliable contraception since raloxifene is contraindicated during pregnancy.

When the patient returned to clinic on March 17, 2010 she reported apologetically that she had a positive home pregnancy test. Pregnancy was confirmed in our laboratory. She was referred to Family Planning Clinic for termination of pregnancy, because, as we re-explained to our patient, raloxifene is FDA Pregnancy Class X (should not be used in pregnancy) and therefore we could not assure her of the likelihood of a healthy baby. Raloxifene was discontinued in the event that she chose to continue the pregnancy.

A repeat brain MRI, performed on April 26, 2010 showed a diminution in the number, size, and viability of the cestodes (Figure 13).

![Figure 13. MRI's showing effect of raloxifene treatment 60 mg/day on a patient with extensive neurocysticercosis](image)

The total number of lesions fell from 37 to 33. Ten lesions shrank, 5 lesions resolved, 18 lesions appeared unchanged, 4 lesions enlarged, and only 1 new lesion appeared. Concomitantly, her serum 1,25-(OH)₂-vitamin D₃ fell from 81 pg/ml to 41 pg/ml (Figure 14), while her serum 25-OH-vitamin D₃ only fell from 34 ng/ml to 30 ng/ml with raloxifene treatment.
On May 5, 2010 she agreed to treatment with a 2 week standard course of albendazole and dexamethasone, which she tolerated well. Rare causes of calcitriol mediated hypercalcemia have been reported and reviewed by Kallas et al. [58] and, although our patient did not develop hypercalcemia, her apparently increased 1-α-hydroxylation of 25-OH-vitamin D₃ may be explained by the same mechanism—either the cestodes themselves or the surrounding host macrophages carrying out 1-α-hydroxylation.

Our patient thus illustrates several previously unknown features:

- Neurocysticercosis cestodes can have several endocrine disrupting effects on their human hosts including: androgenic effects, estrogenic effects, induction of insulin resistance, and enhanced 1-α-hydroxylation of 25-OH-vitamin D₃ either by the cestodes themselves or by the surrounding host macrophages in a process reminiscent of pulmonary sarcoidosis.

- Alteration of the hormonal milieu evoked by the parasites is capable of reversing the induced PCOS in a 2 step process:
  1. the use of metformin reduced the insulin resistance/hyperinsulinemia, which in turn reduced the hyperandrogenism and resulted in restoration of normal menses and resolution of acne and hirsutism, concurrently with an increase in serum SHBG and a normalization of the LH/FSH ratio, but did not, by itself result in restoration of fertility.
  2. addition of the SERM, raloxifene, by causing a less estrogenic milieu restored fertility (although this was an unintended consequence).

- Alteration of the hormonal milieu via the addition of raloxifene to metformin was effective in reducing the parasite burden in a human host. This observation suggests the possibility that alteration of the hormonal milieu may ultimately be found to be a viable primary or adjunctive treatment for various human and veterinary parasitoses.

- Given the burden of widespread cysticercosis, not only in tropical/subtropical areas, but in other area of the globe as well due to increasing migration, cysticercosis may turn out to be an important cause, not only of PCOS, but, ultimately, of the burgeoning epidemic of metabolic syndrome, pre-diabetes, and T2DM.
4. Chapter summary

- Insulin resistance/hyperinsulinemia is a constant feature of both classical and non-classic adrenal hyperplasia as well medication induced/unmasked adrenal hyperplasia.

- In vitro studies suggest that 2 mechanisms for the above observation are gain of 17-α-hydroxylase activity and decrease of 21-hydroxylase activity in the presence of hyperinsulinemia.

- Interventions which reduce insulin resistance/hyperinsulinemia dependably ameliorate the phenotypic/biochemical course of CAH and acquired/unmasked adrenal hyperplasia as they do in PCOS. In the case of NCAH insulin sensitizing interventions eliminate the need for corticosteroids and their attendant side effects, while in classical CAH insulin sensitization shows at least an ability to ameliorate the condition without resorting to supraphysiologic corticosteroid dosages.

- Other drugs and herbals with insulin sensitizing properties may ultimately prove useful in treating CAH.

- Cysticercosis is able to evoke a 4 part endocrine disrupting effect in the human host: insulin resistance, hyperandrogenism, feminization, and enhance 1-α-hydroxylation of 25-OH-vitamin D₃.

- Modifying the cysticercosis-evoked hormonal milieu with the insulin sensitizer, metformin and the SERM, raloxifene is capable of effectively treating cysticercosis induced PCOS, reducing the parasite burden, and reversing the overexpression of 1-α-hydroxylase.

- Serial measurement of vitamin D metabolites may prove to be a fairly economical way of following parasite burden and treatment response compared to serial MRI.

- Cysticercosis may ultimately prove to be a fairly common cause of insulin resistance and PCOS.

5. Nomenclature

CAH-congenital adrenal hyperplasia
NCAH-non-classic congenital adrenal hyperplasia
PCOS-polycystic ovarian (Stein-Leventhal) syndrome
17-OHP-17-hydroxyprogesterone
eGFR estimated glomerular filtration rate
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