Presentation of a Sick Preterm Newborn
By Ann Crickard, DO and Kat Armstrong, PA-S

A 25-year-old G1P0A0 mom with a history of pseudopseudohypoparathyroidism presented to her obstetrician at 35w4d gestation for a routine office visit, and was noted to have decreased fetal heart rate and fetal movement. The mother was admitted to the obstetric unit for admission, and on admission testing was found to have a positive RPR at 1:32. (The mother had a negative RPR at her routine screening appointment 6 months prior to delivery) As the in utero infant was in distress the decision was made to deliver via emergency c-section.

At delivery the 1 minute Apgar score was 6, and resuscitation was initiated with positive pressure ventilation and 70% O2. After 3 minutes the infant was weaned to 35% O2 and CPAP 6 prior to transfer to the neonatal intensive care unit.

On admission to the NICU the infant’s vital signs were as follows:
- Weight 2390 g, (30%ile) Length 43 cm (5%ile) Head circ. 30 cm (5%ile)
- Temp 37C, HR 137, RR 55, BP 46/27, Mean BP 33, O2 sats 98% in CPAP 6 and 35%FiO2
- Significant findings on physical exam include moderate respiratory distress, bilateral subconjunctival hemorrhages, hepatomegaly with liver 5.5 cm below the right costal margin, splenomegaly noted.
- Petechiae are noted over the LLQ of the abdomen, scattered bruising over extremities and posterior thoracic region. There is a subcutaneous calcification over the right anterior tibia.

An admission stat glucose was too low to read, so the infant was started on intravenous D10W with close monitoring of blood sugar (every 30 minutes).

Admission diagnoses:
- Prematurity 35 4/7
- Respiratory distress
- Critical hypoglycemia
- Exposure to primary syphilis with likely intrauterine infection
- Subcutaneous calcification
- Petechiae and bruising
- Hepato/splenomegaly
- Maternal pseudopseudohypoparathyroidism with unknown but likely inheritance

When an infant presents with many issues, it is critical to address the life-saving treatments while at the same time paying attention to the longer term issues that may affect care over the next several hours. With a stable airway and management of the critical hypoglycemia underway, the next steps are to determine what infections this infant may have that will require prompt treatment, as well as endocrine issues that may arise from inherited pseudopseudohypoparathyroidism.

Initial lab evaluation for this infant demonstrated persistent low blood sugar, coagulopathy, liver failure, hyperbilirubinemia, hypocalcemia, and confirmed infection with syphilis (RPR 1:32).

While in the NICU consultations were placed to infectious disease, endocrinology, and genetics.

Infectious disease: The diagnosis of congenital syphilis is becoming more common, and is important to address. Since 2011 there has been a dramatic surge in STI’s, with a concomitant increase in cases of congenital syphilis. There have been at least 1000 cases per year (and rising) in the past several years in the US. These infections are preventable, if infected mothers are identified. At present it is not standard of care to screen mothers for syphilis beyond the first trimester, but screening during the 3rd trimester might prevent some congenital infections. (1,2) Congenital syphilis results in fetal demise in many pregnancies, but when infants do survive to delivery, the long term consequences can be devastating, including rash, especially of the palms, rhinitis, known as snuffles, and thrombocytopenia.

This infant suffered liver failure, with elevated liver enzymes and cholestasis as well as coagulopathy, due to...
inadequate production of clotting factors and likely sequestration of platelets. She was treated with Ursodiol, which reduces the cholestasis secondary to liver failure, and received multiple platelet transfusions. Over the 55 day course of her NICU stay her liver function stabilized and improved and required no further treatment.

The infant in this case was treated with a 10 day course of Penicillin G, to eradicate the treponemal infection. The plan is to repeat the RPR at approximately 3 months of age to ensure full treatment.

**Endocrinology:** This infant was born to a mother with known pseudospeedohyoparathyroidism. It is important to understand the inheritance patterns of this condition. The mother of this infant inherited the condition on the paternal chromosome resulting in a milder presentation of the disorder. Genetic testing of the infant determined the more serious presentation of pseudohypoparathyroidism. Pseudohypoparathyroidism is a genetic disorder caused by a mutation in the GNAS gene in which the body has increased resistance to parathyroid hormone. This in turn causes high levels of parathyroid hormone and phosphorus in the blood, in addition to low levels of calcium. The syndrome commonly occurs in the presence of other hormonal resistance including TSH and GnRH. There are multiple clinical variants of pseudohypoparathyroidism; the most common being type PHP 1A. This type often presents with a constellation of symptoms known as Albright's Hereditary Osteodystrophy which presents as short stature, obesity, intellectual disability, and short hand bones. Patients also present with cataracts, seizures, numbness and tetany secondary to abnormalities in electrolytes. (4)

As a result of the infant's pseudohypoparathyroidism, which is now confirmed to be Type IA she has very high levels of parathyroid hormone (PTH), which remains high because of lack of tissue effect of the hormone (the hormone cannot be down-regulated). This will require monitoring of her calcium and phosphorous levels, as well as addressing the expected defects that will eventually present with bony growth, dentition, overall development, and the neurologic system. This infant was started on ergocalciferol to mitigate the effects of ineffective parathyroid hormone. Ergocalciferol is a Vitamin D analog that increases calcium absorption from the GI tract.

Hyperinsulinemia is a common presentation in preterm or sick newborns. In this infant the hypoglycemia was unrelated to either syphilis infection or pseudohypoparathyroidism. This infant was found to be profoundly hypoglycemic at birth, requiring constant IV infusion of dextrose. She was then started on diazoxide, which reduces the production of insulin by pancreatic islet cells. It functions by opening the K-ATP channels in the cell membranes, altering membrane polarity, reducing calcium flow into the cells, thereby limiting insulin production. The effect of limiting insulin production allows the infant to maintain more normal levels of glucose, but also causes fluid retention, necessitating use of a diuretic to prevent edema. This infant was started on chlorothiazide to counter the effects of diazoxide. (5)

The natural course of hyperinsulinemia is gradual improvement, necessitating close monitoring of blood glucose until it becomes clear that medical management is no longer needed.

In summary, the early clinical course of this very ill neonate required significant medical knowledge, quick turnaround of lab testing and rapid medical decision making. The longer term care for this infant is still in progress, and will require input from multiple specialists, as well as close monitoring in the pediatric medical home.

**References:**

What is hirsutism? It refers to the excessive growth of terminal hair in a male-like pattern in females. Terminal hair is thick, dark hair, in contrast to the more common fine, blonde vellus hair that is seen on many parts of the body in males and females.

How common is hirsutism? It occurs in 5-10% of adolescent girls and premenopausal women. As expected, hirsutism causes significant emotional distress. While the most common cause is polycystic ovary syndrome (PCOS), there are other causes, some of which can be lethal.

In adolescent girls and women (hereafter referred to as simply “women”), terminal hair is usually absent or barely present in the following areas: a) upper lip; b) chin; c) mid-sternum; d) upper and lower abdomen; e) upper and lower back; and f) buttocks. But these are the very areas where the growth of coarse, pigmented hair occurs, growth that defines hirsutism. In fact, hair growth in those areas can be scored to determine both the presence of hirsutism, as well as its severity. This scoring system is called the Ferriman-Gallwey Hirsutism Scoring System, which is shown below in Figure 1.

What causes the growth of coarse, pigmented hair in these sites? In almost all cases, it is caused by an excess of testosterone in the blood. Testosterone in the blood, in turn, is converted to dihydrotestosterone in the hair follicle, and it is the latter hormone that drives the growth of terminal hair.

Both men and women have testosterone in their blood, it is just that it is much higher in men than women. However, a subset of women have abnormal elevations of testosterone compared to the vast majority of women. It is in this subset of women that hirsutism occurs. The other major factor that influences terminal hair growth is genetic endowment. For example, terminal hair growth is least plentiful in Asian women and the most plentiful in women from the Mediterranean or Middle East. And these differences exist even when testosterone levels are completely normal.

What is the source of testosterone in women? About half of the testosterone in women is secreted by the ovary and the other half by the adrenal cortex. However, there are other “male hormones” or androgens in the blood of women.

Two of these are androstenedione and dehydroepiandrosterone. The former is also secreted by both the ovaries and adrenals, while the latter is secreted primarily by the adrenals. However, both androstenedione and dehydroepiandrosterone are easily converted in the body to testosterone.

The causes of hirsutism in premenopausal women are shown in Table 1 below.

### Table 1: Causes of hirsutism in premenopausal women

<table>
<thead>
<tr>
<th>Cause</th>
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<tr>
<td>1. Polycystic ovary syndrome (PCOS)</td>
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<td>2. Idiopathic hirsutism</td>
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<tr>
<td>3. Non-classic congenital adrenal hyperplasia</td>
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<tr>
<td>4. Androgen-secreting tumors</td>
</tr>
<tr>
<td>----- Ovarian</td>
</tr>
<tr>
<td>----- Adrenal</td>
</tr>
<tr>
<td>5. Ovarian hyperthecosis</td>
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<tr>
<td>6. Miscellaneous endocrinopathies</td>
</tr>
<tr>
<td>----- Cushing’s syndrome</td>
</tr>
<tr>
<td>----- Hyperprolactinemia</td>
</tr>
<tr>
<td>----- Hypothyroidism</td>
</tr>
<tr>
<td>----- Acromegaly</td>
</tr>
<tr>
<td>----- Rare syndromes of severe insulin resistance</td>
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<tr>
<td>7. Exogenous androgens</td>
</tr>
</tbody>
</table>

As mentioned above, polycystic ovary syndrome is the most common cause of hirsutism in premenopausal women. In this common condition, most—but not all women—have multiple ovarian cysts. Figure 2 shows a polycystic ovary by ultrasound.
Figure 2: Multiple cysts in a patient with polycystic ovary syndrome

Most patients with PCOS have more than 12 cysts, usually peripherally located, as in the figure.

What causes PCOS? While many elements of the pathophysiology of PCOS have been elucidated, the underlying cause is unknown. However, there are a vast array of abnormalities other than cystic ovaries. For example, luteinizing hormone (LH) levels are too high. This high level stimulates theca cells in the ovary to secrete too much testosterone. In addition, there is no mid-cycle surge of LH to trigger ovulation. Failure of ovulation can cause infertility, and lead to irregular menstruation. Another abnormality is the presence of cellular resistance to insulin, which in some cases can lead to Type 2 diabetes. Finally, while some of those with PCOS are lean, a significant number are overweight or obese.

Non-classic congenital adrenal hyperplasia (NCCAH) is uncommon, but when present, can cause hirsutism. This condition can present in infancy or much later. It is “late onset” NCCAH that can manifest as hirsutism in premenopausal women. NCCAH involves a complete or partial deficiency of the enzyme 21-hydroxylase. When this enzyme is deficient, cortisol synthesis is initially impaired. However, homeostasis ensures normal cortisol levels by overdriving the adrenal with ACTH. This overdriving of the adrenal increases their secretion of androgens.

Most ovarian tumors arise from epithelial cells; however, there are uncommon tumors that arise from hormone-secreting cells, such as theca cells. In these patients, testosterone blood levels are very high, much higher than in PCOS. These levels not only cause severe hirsutism, but can cause the physical changes of virilization. Virilization includes: a) breast atrophy; b) enlargement of the clitoris, called clitoromegaly; c) lowering of pitch of voice; and d) male-pattern baldness. It is important to diagnose these tumors because they can metastasize and lead to death.

Adrenal tumors can also cause hirsutism, or hirsutism and virilization. If, in addition to androgens, an adrenal tumor secretes excessive amounts of cortisol, the clinical picture is one of Cushing’s syndrome. Ovarian hyperthecosis is not a common cause of hirsutism in premenopausal women; rather, it more commonly presents after menopause. In this condition, nests of non-malignant cells (luteinized theca cells) secrete large quantities of testosterone. Thus, these patients often have both hirsutism and virilization.

An assortment of other endocrine diseases can sometimes present with hirsutism or be associated with hirsutism. Any cause of Cushing's syndrome can do so, as can hypothyroidism and hyperprolactinemia. Many medications can cause hyperprolactinemia, but the most common cause in premenopausal women is a prolactin-secreting pituitary tumor.

Finally, in women who take exogenous androgens, such as testosterone, dehydroepiandrosterone, or danazol, hirsutism can occur.

Once a woman is clinically found to have hirsutism, the cause must be determined. Assuming the patient is not taking exogenous androgens, it is important to document whether or not oligomenorrhea or amenorrhea is present. In women with menstrual abnormalities, blood work is needed to quantify testosterone level, and exclude pregnancy, hyperprolactinemia, hypothyroidism, non-classic congenital adrenal hyperplasia, and premature ovarian failure. Appropriate tests are shown in Table 2.

Table 2: Initial blood tests in premenopausal women with hirsutism AND irregular menstruation

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Diagnostic possibility</th>
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<tr>
<td>Total testosterone</td>
<td>Many causes</td>
</tr>
<tr>
<td>hCG</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>TSH (thyroid stimulating hormone)</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>FSH (follicle stimulating hormone)</td>
<td>Premature ovarian failure</td>
</tr>
<tr>
<td>8 am serum 12-hydroxyprogesterone</td>
<td>Non-classic congenital adrenal hyperplasia</td>
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</table>

For premenopausal women who have hirsutism but who retain normal menstruation, simply measuring total testosterone is sufficient biochemical workup. This is true even in women who are taking oral estrogen-progesterin contraceptives (OCs) or related patches or vaginal rings.
The exact testosterone level is crucial, and not all labs have highly sensitive assays. Thus, discussing appropriate labs with an endocrinologist is warranted.

After obtaining the initial bloodwork, if the only abnormality is an elevation of testosterone, the patient very likely has PCOS—unless the testosterone level is greater than 150ng/dL. This level in a woman suggests the presence of an ovarian tumor, adrenal tumor, or ovarian hyperthecosis. Imaging is then the next step.

The normal level of testosterone in women is less than 45-60 ng/dL. Those with PCOS have levels greater than 45-60 ng/dL but less than 150ng/dL.

"Idiopathic hirsutism" is the name given to those in whom all bloodwork is normal. In these cases, it is thought that their hair follicles are hypersensitive to testosterone. That is, their hair follicles are stimulated to produce coarse pigmented hair in response to normal blood levels of testosterone.

Treatment of hirsutism itself is straightforward. But most patients with hirsutism have PCOS which requires comprehensive treatment above and beyond that for hirsutism. In those with PCOS, it is important to treat any associated overweight or obesity, hypertension, diabetes, menstrual irregularities, and infertility if desired.

With respect to hirsutism, there are two arms of therapy: a) hormonal treatment; and b) physical removal of hair. Hormonal treatment is recommended first to decrease hair growth. However, this takes many months—at least 6 months to see an effect. Starting hormonal treatment first makes physical hair removal more successful.

There are two mainstays of hormonal treatment: a) oral estrogen-progesterone contraceptives OC's); and b) anti-androgen treatment.

Unless a woman has contraindications to OC's or desires to become pregnant, OC's are considered first-line treatment. OC's raise estrogen and progesterone levels in the blood, and these increases, in turn, inhibit pituitary secretion of LH and FSH. Lower levels of these gonadotropins results in less secretion of androgens by the ovaries.

In addition, the elevated levels of estrogen and progesterone, in turn, increase the concentration of sex-hormone binding globulin (SHBG). Most sex hormones in the blood, including testosterone, exist in the blood bound (or carried) by SHBG. However, a tiny fraction of sex hormones exist in the "free" or non-bound state. It is important to understand that it is only the free hormone that is available to stimulate terminal hair growth.

Thus, OC's decrease the fraction of free testosterone by decreasing the total secretion of testosterone by the ovaries. It is this drop in free testosterone that decreases terminal hair growth. How effective are OC's in the treatment of hirsutism in PCOS? Hirsutism significantly improves in 60-100%. As mentioned above, when OC's are started, the effect on hair growth is not assessed until at least 6 months. At that time, if hair growth has improved, OC's are continued. On the other hand, if the response is poor, the next step is to add an androgen blocker.

The primary androgen blocker used in hirsutism is spironolactone. This medication blocks the action of testosterone at the level of the hair follicle. Spironolactone also competes with dihydrotestosterone binding to androgen receptors.

It is important to understand that spironolactone can only be used if it is not contraindicated, and it is contra-indicated in all women who might become pregnant. Thus, in women who are not already on OC's, spironolactone can only be used if other methods are employed to prevent pregnancy.

In women with idiopathic hirsutism—who have normal testosterone levels—spironolactone is the mainstay of hormonal treatment as long as pregnancy is prevented.

In addition to hormonal treatment, there are many methods of physical hair removal. The best outcomes usually occur when hormonal treatment is combined with physical hair removal.

In electrolysis, a slender probe is inserted into the hair follicle. The generated heat destroys the growth center and the hair is easily removed with tweezers. View an example of electrolysis here.

Another method of hair removal is via laser. There are an array of laser methods, many of which can remove multiple hairs at once. View an example of laser hair removal here.

References:


Patients and providers have little say when it comes to choosing between a brand or generic medication. Insurance companies typically will not pay for a brand name drug when a generic is available. If a patient prefers the brand name, they can choose to pay out-of-pocket and bypass insurance. While this is an option, it may not be a viable one. For example, a typical 30-day supply of the popular blood pressure medication, losartan 50 mg, costs around $9.1 Cozaar®, the brand of losartan, runs close to $120 for the same 30-day supply. Even when a patient is willing to pay for a brand name product, overhead costs prevent most pharmacies from readily stocking brand name drugs when there are generic equivalents on the market. In the end, most patients receive generic medications due to the quick availability and lower price. It is important to note that there may be multiple generic manufacturers for one specific drug as well. Going back to losartan 50 mg as an example, there are 20 different manufacturers. It is possible a patient could receive a different manufactured version of losartan 50 mg every month for nearly two years!

Despite the wide use of generic medications, concerns regarding their quality, safety, and efficacy challenge patients and providers. The idea, "you get what you pay for," as well as the status of other brand name products in society may lead people to think generic drugs are inferior. Patients have reported negative effects following generic substitution, leading to further mistrust of the products. Recently a carcinogen, NDMA (N-nitrosodimethylamine), was found in several generic prescription and over-the-counter drugs, casting further doubt on the safety of generics. Healthcare providers and patients questioned how a contaminant entered not one but several different medications in such a highly regulated drug industry.

The version (manufacturer) of a generic medication that patients receive is difficult to control. We also cannot control, or even be certain of, the manufacturing processes occurring at thousands of plants worldwide. We cannot force insurance companies to cover brand name medications and we cannot expect that our patients should pay brand name prices. So, what do we do to ensure patients receive the best care possible when so many things lie outside of our control? Listen to your patients. Believe them when they say a specific generic does not seem to work as well for them. Adjust doses appropriately when needed. Specify brand name required when you feel any variation in the dose may cause therapeutic failure. Educate patients that while there have been isolated incidents with generic drugs, overwhelmingly we use these products with success. Let them know that you will work with them to meet their goals of therapy, regardless of the product they receive at the pharmacy. In addition, whenever you can, speak up for stronger drug manufacturing oversight whether through the FDA or independent agencies.
Because of COVID, we never resumed normal educational experiences. The remaining semester and half of didactic year were conducted online. As students, we had to adapt our home environments to accommodate the world of PA school. We transformed our kitchen tables and sofas into desks and chairs. Our cats became our study partners. Our children now outranked the window-washers for the biggest distraction during class. Husbands and roommates became our simulators and standardized patients as we battled to learn the art of physical exam without the guiding hands of a well-practiced provider. We struggled through connectivity issues and time zone differences.

Because of COVID, our support systems were rattled. The closing of businesses across the state robbed churchgoers of their in-person Sunday morning fellowship, gym rats of their healthy routines, and students of their Starbucks study spots. Those of us who moved to Columbus for school now faced unfamiliar and unnatural isolation. Social distancing restricted our already limited ability to visit our family and friends in a time when their support was most needed. We attended virtual weddings. Normal activities now required excruciating deliberation. The decision to attend the funeral of our own sweet classmate was accompanied by a painful consideration of risks. The craziness in our personal lives persisted. We have experienced loss of friends and family, bad news, and housing struggles.
Because of COVID, we have faced so many unknowns. How do we learn medicine online and socially distanced? Will our rotation sites remain open? Will our clinical experiences be limited by COVID policies? When will we graduate? When our rotation location gets moved to a different state last minute, where will we live? How can we safely celebrate the holidays without endangering our loved ones and risking our health and educational opportunities?

But because of COVID, we have grown. We pushed through Zoom-fatigue. We learned how to manage high levels of stress. We adapted to non-ideal situations. We learned that strength does not mean ignoring the losses we experienced and that self-care can look like shedding a few tears and going for a walk. When school, life, and family demand so much from us, we learned to give ourselves grace. We identified those blessed people in our lives that will truly be there for us. We dug deep to find every ounce of inner strength and courage we have. We learned resilience and gained perspective of the bigger picture. We have a new appreciation for health, hugs, and smiles.

Since March of 2020, we have endured loss, unknowns, sacrifice, stress and disappointment. But we have also experienced grace, friendship, gratitude, and resilience...because of COVID.