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QUESTION 1: Discuss the water and electrolyte metabolism of parathyroid hormones, calcitonin, Vit D and calcium

1. PARATHYROID HORMONE

Parathyroid hormones are very important endocrine hormone regulator when it comes into regulation of the calcium and phosphorus levels in extracellular fluid. Parathyroid hormone is secreted from the four parathyroid glands located behind the thyroid gland. These hormones are able to regulate the calcium level within the extracellular fluid via targeting the cells located in the kidneys, the intestine and bones. When secreted, as a preprohormone, it undergoes modifications before it is released to the target cells to control calcium level through suppression of calcium loss in the urine, mobilization of calcium from bones and lastly enhancing the absorption of calcium from the intestines.

1. Suppression of Calcium loss in Urine

Urinary calcium excretion is a mainly affected by the filtered load of calcium determined by plasma calcium level when the glomerular filtration is constant and the level of the circulating parathormone (Rajesh, 2016). The parathyroid hormone controls the renal calcium excretion and can be observed in cases of hyperparathyroidism and hypoparathyroidism and the reduced calcium renal elimination after introducing the PTH into normal individuals. The hormone suppresses the renal elimination of the calcium via the c TAL, the distal convoluted tubule and the connecting tubules. In case of the mutation on the receptor for vitamin D in the kidney nephrons, 1, 25(OH)2D is a requirement to enable the calcium resorptive response to the PTH. The mechanism of PTH action involves the activation and the acceleration of the transcellular transport by way of stimulating paracellular, diffusional calcium transport through augmenting the transepithelial voltage gradient (Encyclopedia of Endocrine Diseases, 2004). The level of water must be regulated through the regulation of the absorption and excretion of the sodium and chloride ions and the potassium ion depletion because the extracellular fluid volume expansion is an active agent in the elimination of the calcium ion via the renal excretion.

1. Mobilization of calcium from bones

Parathormone cause bone calcium absorption in two main steps, the rapid step phase and the slow phase. The first phase is rapid because it is an activation of the already existing but dormant osteocytes to enhance the rape of absorption of calcium and phosphorus. This is observed when doses of parathormone are injected revealing increased calcium ion concentration in blood. Histological examination has proved that the calcium come from the bone matrix within the osteocytes and from the osteoblast within the bone surface. The osteocytes and the osteoblast from a system called osteolytic-membrane system that separate the bone from the extracellular space and also hold a fluid called bone fluid from which this system pumps calcium ion into the extracellular space. This system pump, pumps calcium ion out of the bone rapidly when active and can lead to osteolysis and when it is inactivated the level of calcium in the fluid rises. The action of this system pumps is made possible because of the PTH receptors within it. The second phase which is the slow phase occur as a result of the activation of the osteoclasts. The effect is achieved in two ways because these osteoclasts have no PTH receptors. Exposure of excess PTH for a long time, initiate immediate activation of osteoclasts already formed and also bring about the formation of new osteoclast. This exposure leads to reabsorption of calcium and calcium int the bone matrix and stoppage of the PTH exposure reverse the process. This is controlled hormonally and when appropriate to balance the electrolyte level in the blood stream.

1. Intestinal Calcium Absorption

The transcellular Ca2+ absorption is nutritionally and physiologically regulated and is an energy dependent process. Parathyroid hormone regulates the absorption of Ca2+ in the intestine via the Calcium-PTH-vitamin D feedback loop. The effect of parathyroid hormone in intestinal calcium absorption is seen indirectly through the apical vitamin D-dependent calcium entry via the transient receptor potential cation channel. The level of the calcium concentration in the plasma is a consideration of the component of the negative feedback regulation to suppress the parathyroid hormone release and production of the 1, 25-dihydroxycholecalciferol and hence slow down the calcium absorption rate. Parathyroid hormone stimulates the transcription of the gene CYP27B1, a gene for renal enzyme 1α-hydroxylase, and suppress the gene CYP21A1, a renal enzyme tasked with degradation of the 1, 25-dihydrocholecalciferol (Clemens, Bilezikian, Martin and Rosen, 2019) and this elevate the plasma levels of these calciferols and hence elevated rate of intestinal calcium absorption. PTH also has a direct positive role in intestinal calcium absorption. The N-terminal fragment 1-34 of the PTH, stimulate the intestinal absorption of calcium alongside the PTH 1 receptors in the basolateral membrane of the intestines especially in rats, suggesting the direct influence of PTH on the intestinal Ca2+ absorption.

This hormone controls the water level by regulating g the absorption of other ions like potassium, chloride and bicarbonate, the latter being via a rapid non-genomic process (transcaltachia). These ions increase the reabsorption of water into the blood stream as they get absorbed across the concentration gradient.

Clinical Correlation

Parathyroid hormone condition can manifest in two ways; primary and secondary hyperparathyroidism which occurs as a result of excessive secretion of the parathyroid hormone to control the level of the calcium and the fluid concentration in the plasma. Primary hyperparathyroidism can arise as a result of the adenoma which is tumor of the parathyroid glands and leads to secretion of the parathyroid hormone with insignificant regulation of the hormones. This leads to elevation of the calcium in the plasma (hypercalcemia), decalcification of bone and formation of kidney stones. Secondary hyperparathyroidism arises due to malfunction of other organs other than the parathyroid glands leading to the over secretion of parathyroid hormones. A good example is the kidney disease in which the kidneys cannot properly absorb the calcium in the urine and this is compensated with elevated levels production of the parathyroid hormone levels. Also, the inadequate provision of calcium also can lead to the secondary hyperparathyroidism. This condition can cause decalcification of bones leading to easy fractures and. These ultimately leads to imbalance of the water and electrolyte balance.

Hypoparathyroidism can also occur causing decreased parathyroid hormone production and hence hypocalcemia and elevated levels of phosphorus in blood. This condition can arise following surgical removal of the parathyroid glands and destruction of the parathyroid glands by disease like adenoma and hyperplasia and can cause frequent tetany and convolution.

Treatment

Treatment of hypoparathyroidism can be done via calcium infusions, oral vitamin D and calcium supplement therapy. The diagnosis can be done by checking the serum level of the calcium ion and the parathyroid hormone.

1. CALCITONIN

Calcitonin or the thyrocalcitonin is a hormone produced by the thyroid gland cells alco called the C cells. It is made up of 32 amino acids with a molecular weight of not less than 3400. It is coded by a gene that also codes the neuropeptide; calcitonin gene related peptide (CGRP). The action of calcitonin on the regulation of electrolyte is seen in its action on the control of the calcium blood level via prevention of excessive bone resorption. Calcitonin performs its action of calcium balance through action on bones and action on kidneys.

1. Action on bones

When calcitonin interacts with its receptors on the osteoclast surfaces, there is geometrical increase in the formation of the cyclic AMP and this almost instantly diminishes the activities of the ruffled borders. The influence and the effect of the calcitonin and the parathyroid hormones on their respective receptors shows similar effect and show some similarities in the amino acid of sequences in the receptors. However excessive calcitonin stimulation brings about down regulation of the receptors interfering with their ability to influence calcium reabsorption.

1. Action on kidneys

High concentration of calcitonin increases renal excretion of the calcium ions through direct action on the proximal tubules. This can lead to hypocalcemia though in human its is easily managed by the balance with the PTH. In case of thyroid tumor secreting large amount of calcitonin, the action of the kidney is not affected.

1. VITAMIN D

The derivative of vitamin D3 is crucial for the maintaining adequate concentration of the calcium in the extracellular fluid and adequate bone mineralization of the bone matrix. The overall physiological action of the vit D is the increase of electrolyte concentration in the extracellular fluid through calcium and phosphorus. These are extracted from the intestine, kidney and bone.

1. Action on kidney

Vitamin D work hand in hands with the 1, 25(OH)2D3 and the latter is very crucial in the absorption of the calcium and phosphate from the glomerular filtrate in case of Vitamin D deficiency. The hormone parathyroid is increased in case of the Vitamin D deficiency and this lowers the reabsorption of phosphate ions. When the 1, 25(OH)2D3 is increased, the secretion of the PTH is decreased and hence proximal tubular reabsorption is enhanced. The receptors for the 1, 25(OH)2D3, are located in the distal nephron, in the same cells in which the PTH stimulates calcium uptakes and express the same vitamin D dependent proteins same as those in the intestinal.

1. Action on bone

Deficiency of Vitamin D is always associated with the decreased mineralization of the bones. The precursor 1, 25(OH)2D3, is although nit directly involved with bone formation and calcium phosphate deposition on osteoid. Increased electrolyte concentration increases the mineralization in bones and then ultimately increases the bone mineralization. The mineralization of the bone s can be increased through the dietary intake and absorbed through the intestine in case of deficiency or the vitamin D receptors. 1, 25(OH)2D3  act on the bone to promote the resorption of calcium in the same manner as the PTH, through increasing the activity and the number of osteoclasts. 1, 25(OH)2D3  and PTH stimulate the osteoblastic cells to show the m-CSF and RANK ligand as well as a variety of other proteins.

1. CALCIUM

High calcium level in plasma act as a hormone like action and this makes calcium a fourth calciotropic hormone. Higher calcium concentration has a more evident effect on the blood plasma than the calcitonin and this lower the calcium level. About twenty five percent of the filtered calcium is reabsorbed by the thick ascending loop of Henle driven by the positive luminal voltage created as a consequence of active reabsorption of sodium chloride. The basolateral surface of the thick ascending loop of Henle’s expresses the same calcium sensing receptors as the parathyroid chief cells. The receptors couples with both Gαi and the Gαq and when activated c AMP formation and increases production of DAG and IP3 and this result in the diminution of the protein kinase A activity and lowers its stimulatory actions on the sodium/2 chloride/potassium cotransporter. This increases the DAG which further activates the protein kinase C which phosphorylate and decreases the activity of the ROMK channel, which are renal outer medullary potassium. These activities effect the reabsorption of both sodium chloride and calcium and because of the limited capacity of the downstream calcium reabsorption mechanisms leading to more loss of calcium in urine and plasma level of the calcium the fall. The alteration of the sodium and chloride ions affect the absorption rate of water.

QUESTION 2: Discuss inherited Disorders in Steroid Hormone Metabolism

Steroid hormones perform important roles in the regulation of the salt and water balance, energy metabolism, stress response and the initiation and the maintenance of the sexual differentiation and the reproduction. They are formed from pregnenolone, a precursor from cholesterol and the synthesis occurs in the mitochondria. Adrenal glands, placenta and the gonads are the principle steroidogenic organs. The metabolism of the steroid with the initial step involving the reduction of the double bond to leading to the formation of the tetrahydro derivatives. Genetic disorders in steroid metabolism arise as a result of mutation in the genes associated with either pathway enzymes, receptors or even the manufacture of some of the inter- mediate. This condition can be discussed as;

Congenital Adrenal hyperplasia

This is a group of genetic disorders that affect the adrenal glands and hence affect the production of the steroid hormones. This condition always arises as a result of lack of the enzyme 21-hydroxylase, an enzyme responsible for the formation of the aldosterone and cortisol. This condition is associated with elevated levels of the androgens since the precursors of the aldosterone and cortisol synthesis get shunted to the pathway for the production of the androgen. CAH has no cure but proper treatment can be done to manage the condition.

The mode of transmission of CAH is autosomal recessive and 90% of CAH is due to the 21-hydroxylase while the remaining is caused due to the 11β hydroxylase deficiency

Causes

Deficiency of aldosterone is related with hyponatremia due to excessive loss of Na+, and also hyperkalemia, which is related with K+ elevation in blood stream and these all lead to hypotension.

Deficiency of cortisol is associated with hypoglycemia and elevated ACTH

Symptoms

* Low blood pressure
* Virilization in female; clitoral enlargement, early puberty
* Normal sexual development in male.

CAH can be diagnosed through measuring the serum level of 17-hydroxy-progesterone which elevation above the normal level is an indication of CAH. The serum level of cortisol and aldosterone will be below the normal level.

Treatment

This involves hormone replacement therapy of the cortisol with hydrocortisone and aldosterone with fludrocortisone.

Lipoid congenital adrenal hyperplasia

This is an uncommon form of an endocrine disorder form of the congenital adrenal hyperplasia and the most lethal. It begins at the early stages of the steroid hormone synthesis, specifically from the transportation of the cholesterol into the mitochondria and the conversion of cholesterol into the pregnenolone, which is the precursor of all the steroid hormones. This condition leads to the deficiency of the mineralocorticoids in an affected infants and children. Affected Male have feminine looking genitals due to the excessive under-virilization. The adrenals are enlarged by the accumulation of the lipid globules obtained from the un-transported cholesterol. This condition is inherited in an autosomal manner. The presentation of this condition can be divided into four groups.

Presentation

1. Mineralocorticoid deficiency

This can be detected after two weeks to three months of age majorly after significant weight loss, vomiting and dehydration with hyperkalemia, hyponatremia and the metabolic acidosis

1. Glucocorticoid deficiency

Insufficient production of the corticoid synthesis has many consequences with elevation of the ACTH being accompanied by and contributed by a marked hyperpigmentation even in the newborn. Inadequate cortisol hasten stress and increases the hypoglycemia and contribute to the high mortality rate in infants.

1. Sex steroid deficiency and the gonads damage caused by the lipid accumulation

The prenatal production of the Dehydroepiandrosterone (DHEA), when impaired in the fetal adrenal gland leads to abnormally low levels of the maternal estradiol by the middle of the pregnancy. It is realized in female after the development of the salt-wasting adrenal crisis or any condition of progressive adrenal insufficiency. The male genitals are affected by the lipoid CAH are severely under-virilized due to the impairment of the steroid hormone synthesis. The fetus testes manufacture Anti-Mullerian Hormone (AMH) which hinder the formation of the uterus and inner vagina from forming and since the Leydig cells cannot make enough testosterone during development, the testes remain in the abdomen or lodged in the inguinal canals and are rendered unfunctional. These male does not go into puberty and will remain infertile. The development of penis is also affected.

Diagnosis

The diagnosis of lipoid CAH can be done through gene sequencing.

The management of the Lipoid CAH

Glucocorticoids can be provided at minimal amount and for stress management. Affected female may need estrogen replacement at or after puberty. A successful trial for the management of the late onset lipoid CAH due because of the StAR deficiency was the application of the hormone replacement therapy in combination with assisted fertility techniques like the intracytoplasmic sperm injection and this was followed by a successful ovulation and implantation and birth. Most affected men are undervirilized such that they are raised as girls. The testes are removed due to the risk of the development of cancer.

Congenital adrenal hyperplasia due to the deficiency of the 3β-hydroxysteroid dehydrogenase deficiency

This is an uncommon form of the CAH that result from mutation in the gene involved with the synthesis of the cortisol by the adrenal gland, the 3β-hydroxysteriod dehydrogenase (3β-HSD) type II (HSD3B2). This leads to the accumulation of the 17α-hydroxypregnenolone. The presentation of this condition ranges from mild to severe. The most common form of severe manifestation can be observed in infants as salt wasting because of the loss in the mineralocorticoids. Mild manifestations can be observed as virilization in females and undervilirization in male victims but is not associated with adrenal crisis. This is the only form of CAH that can cause ambiguous genitalia in both genders.

Diagnosis

Suspicion of this condition is raised following the appearance of genitalia at birth or by development of the salt wasting crisis during the first month of life. The presence of elevated renin, DHEA, 17α-hydroxypregnenolone and pregnenolone is a confirmation of the condition.

Management

The management of this condition are similar to the 21-hydroxylase deficiency and involve;

* Replacing mineralocorticoid with fludrocortisone.
* Suppressing DHEA and replacing cortisol with glucocorticoid
* Providing extra glucocorticoid for managing stress

It is also worth noting that children with 3β-HSD CAH unlike the CAH may be unable to produce adequate amount of testosterone for boys and estradiol for girls to alter their pubertal changes.

Congenital adrenal hyperplasia due to 17α-hydroxylase deficiency

This leads to the decreased production of the cortisol and sex hormones but elevates the synthesis of the aldosterone. It results as a result of defect on the gene CYP17A1, a gene responsible for encoding of enzyme 17α-hydroxylase

Symptoms

* Hypercortisolism
* Ambiguous genitalia
* Hypokalemic hypertension

It is inherited in an autosomal recessive manner.

Management

This condition can be managed through replacement of the mineralocorticoids with glucorticoids. For affected female, estrogen is provided to induce puberty and periodic supplements of progestin to regularize menses. Fertility is always reduced because egg maturation and ovulation are poorly supported by the reduced intra-ovarian steroid production.

Hypospadias can be replaced by surgery, salvaging the testes with orchiopexy whenever possible and the testosterones be replaced so that the puberty may occur throughout life.

Isolated 17, 20-lyase deficiency (ILD)/ Isolate 17, 20-desmolase deficiency

This is a rare endocrine and autosomal recessive genetic disorder which is associated by a complete or partial loss of 17, 20-lyase activity and leads to impaired production of androgen and estrogen sex steroids. This condition manifest as partially or fully underdeveloped genitalia (pseudo-hermaphroditism) in males considered intersex and in both sexes as a reduced or absent of secondary sexual characteristics leading to a child-like appearance in adulthood if left untreated.

Signs and symptoms

* Pseudo-hermaphroditism

Corticosterone methyl oxidase deficiency

This disease is also called aldosterone synthase deficiency and is associated with hyponatremia and hyperkalemia usually in the first few weeks of life. Individual with this kind of condition may experience high level of acid in blood (metabolic acidosis). This corticosterone methyl-oxidase deficiency occurs in two forms; type I and type II. These forms have similar signs and symptoms but it they can be distinguished through laboratory testing. Corticosterone methyl-oxidase deficiency is transmitted in an autosomal recessive manner. Parents who are carriers present with no signs and symptoms of the condition.

Signs and symptoms

* Vomiting
* Dehydration
* Low blood pressure
* Extreme tiredness and muscle weakness
* Affected infants often experience failure to thrive

Causes

This condition is caused by the mutation on CYP11B2 gene which instruct the manufacture of the aldosterone synthase in the adrenal gland. This enzyme is involved in the production of the aldosterone that is concerned with the regulation of the blood pressure by maintaining proper fluid and salt in the blood. Excessive amount of the salt in form of the Na+ and Cl- leaves the body will K+ get accumulated and the resulting ionic imbalance in the body, underlies the signs and symptoms of corticosterone methyl-oxidase deficiency. Furthermore, defects in the inactivation of the cortisol such as the 11β-hydroxysteroid dehydrogenase type II deficiency can also lead to hypertension with hypokalemia in absence of elevated levels of mineralocorticoids.

Abnormalities due to glucocorticoids and mineralocorticoid receptors

Mineralocorticoid and the glucocorticoid play an important role in physiological function by regulating growth, development and maintenance of homeostasis which are coordinated by their receptors. The defects in the receptors, importantly insensitivity of the receptors to certain enzymes during steroidogenesis can be classified into four based on the insensitivity to a particular enzyme as follows;

1. Gonadotropin-releasing hormone insensitivity

This condition, also known as the Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD), is an autosomal recessive genetic and an endocrine syndrome associated with the inactivation or mutation in the Gonadotropin-releasing hormone receptor leading to its insensitivity to the hormone gonadotropin-releasing hormone resulting to the inability of the gonads to synthesis sex hormones.

Signs and symptoms

It is important to note that GnHR insensitivity can present at any age though sign and symptoms presentation are subject to the age-related period of reproductive activity.

* Boys with more severe cases of GnHR in neonatal period present with microphallus and cryptorchidism believed to be as a result of neonatal GnHR deficiency. Majority of boys with micro phallus are often diagnosed with GnHR insensitivity as compared with girls whose GnHR insensitivity does not affect reproduction. Though congenital nonreproductive features like midline facial defects and skeletal abnormalities may be present in both sexes.
* Patients may present, for both sexes, with GnHR insensitivity with failure to commence sexual maturation i.e., primary amenorrhea in girls and lack of virilization in boys and also failure to establish pubertal growth spurt. However, some patients may present successful initiation of sexual maturation and pubertal growth spurt but later ceases, female may present thelarche and menarche but later the development of hypogonadotropic hypogonadism.
* It also causes the IHH, if it does present not with the anosmia.

Causes

The causes of GnHR insensitivity can be grouped into to broad categories

* Congenital causes

1. Kallmann syndrome:

This affect genes like ANOS1, SOX10, IL17RD, SEMA3A etc.

1. Digenic and Oligogenic Mutation

Involves A heterozygous FGFR1 mutation and heterozygous deletion in the NSMF gene.

1. GnHR deficiency associated with mental retardation or obesity
2. Congenital malformation associated with craniofacial anomalies
3. Laurence-Moon-Biedl syndrome

* Acquired causes

1. Benign tumors and cysts
2. Craniopharyngiomas
3. Metastatic tumors
4. Chronic systemic diseases
5. Drugs

Treatment

The choice of therapy is arrived at based on the current bone age, psychosexual needs, predicted adult height and current height percentiles. Exogenous estrogens are used for girls in prepubertal age to build and sustain normal bone and muscle mass. The administration of the estrogen can be either transdermal or oral followed by progestin which prevent endometrial hyperplasia, though cure should be taken to ensure that it is not added prematurely which might interfere with breast development. Administration of testosterone, exogenous gonadotropin, or the GnHR therapy can be performed on boys. Testosterone induce pubertal growth while the remaining medication induce spermatogenesis. The oral testosterone is not used because of its hepatic toxicity.

1. Follicle-stimulating hormone insensitivity

This condition, also called ovarian follicle hypoplasia or granulosa cell hypoplasia, is a rare autosomal recessive genetic and an endocrine syndrome which have much significant effect on female patients than male counterparts. It is as a result of the insensitivity of the follicle stimulating hormone, a gonadotropin, effects which usually stimulate the production of estrogen by the ovaries and the maintenance of the fertility in both female and males.

Signs and symptoms

This condition in females present in two major forms

* Hypoestrogenism/ hypergonadotropic hypogonadism

This is as a result of delayed or absent puberty and associated physical changes leading to sexual infantilism and if left unattended to result into reduced uterine volume and osteoporosis.

* Ovarian dysgenesis

This leads to primary or secondary amenorrhea, infertility and slightly enlarged ovaries. The males do not show serious symptoms or signs but, may present partial or in rare occasion complete infertility with reduced testicular volume and oligozoospermia-spermatogenesis.

Causes

Follicle-stimulating hormone insensitivity is caused by the mutation of the follicle stimulating hormone receptor (FSHR) hence altering the receptor-hormone interaction. This alters the ability of the granulosa cells and the ovarian follicles to respond to the hormone FSH resulting in the lowered production of estrogen leading to loss of menstrual cycle and the inability of the Sertoli cells within the seminiferous tubules of the testes to respond to FSH hence impaired spermatogenesis. This condition is similar to the Luteinizing Hormone insensitivity with the exception that LH insensitivity affect males the most.

Treatment

This condition can be managed by hormone replacement therapy with estrogen

1. Leydig Cell Hypoplasia

This condition is an autonomic recessive genetic and endocrine syndrome characterized with the inability of the body to respond to the Luteinizing hormone, a gonadotropin responsible for the signaling of the Leydig cells of the testes to respond to the hormone testosterone and androgen sex hormones. Leydig cell hypoplasia does not occur in females because they do not have the Leydig cells of testes although the cause (luteinizing hormone insensitivity) does affect female with manifestation through primary amenorrhea, infertility and ovarian cysts.

Signs and symptoms

Pseudo-hermaphroditism is the main sign and symptom of this condition and is associated with; feminized, ambiguous relatively underdeveloped external genitalia, gender variance, absent puberty, absent bone maturation and osteoporosis

Causes

Leydig cell hypoplasia is caused by mutation in the gene LHCGR which is responsible for the encoding of the LH/h CG receptor. The reduced response of the h CG receptor to respond to the LH, leading to reduced number of the Leydig cells lower than the normal androgen level, causing testicular atrophy. In situation where there is complete insensitivity of the Leydig cells to LH, the production of the androgen by the testicle is greatly reduced leading to no secondary characteristic development.

Treatment

Treatment can be done by hormone replacement therapy with androgen which leads to normal sexual development and the resolution of most of the symptoms. Surgical correction may be performed n the genitals and orchidopexy may be performed if need be.

1. Familial male-limited precocious puberty

Familial sexuality precocity or gonadotropin-independent testotoxicosis, is a form of gonadotropin- independent precocious puberty affect male and present with early onset of puberty. This can present even as early as 1 year of age. It has an autosomal dominant pattern of inheritance and only affect male. Females are not affected. The mutant gene affect the Luteinizing hormone (LH) receptor. Short spinal length may be observed in boys due to the rapid advancement in the epiphysial maturation.

Treatment can be by administering drugs that suppress gonadal stereogenosis i.e., cyproterone acetate, ketoconazole, spironolactone and the testolactone. The use of androgen receptor antagonist bicalutamide and the aromatase inhibitor anastrozole can be applied as well.

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