In molecular biology, human chorionic gonadotropin (hCG) is a hormone produced by the syncytiotrophoblast, a portion of the placenta, following implantation. Some cancerous tumors produce this hormone; therefore, elevated levels measured when the patient is not pregnant can lead to a cancer diagnosis. However, it is not known whether this production is a contributing cause or an effect of tumorigenesis. The pituitary analog of hCG, known as luteinizing hormone (LH), is produced in the pituitary gland of males and females of all ages. As of December 6, 2011, the United States FDA has prohibited the sale of "homeopathic" and over-the-counter hCG diet products and declared them fraudulent and illegal.

Structure

Human chorionic gonadotropin is a glycoprotein composed of 237 amino acids with a molecular mass of 25.7 kDa. It is heterodimeric, with an α (alpha) subunit identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and β (beta) subunit that is unique to hCG.

- The α (alpha) subunit is 92 amino acids long. [8]
- The β-subunit of hCG gonadotropin (beta-hCG) contains 145 amino acids, encoded by six highly homologous genes that are arranged in tandem and inverted pairs on chromosome 19q13.3 - CGB (1, 2, 3, 5, 7, 8). [9]

The two subunits create a small hydrophobic core surrounded by a high surface area-to-volume ratio: 2.8 times that of a sphere. The vast majority of the outer amino acids are hydrophilic. [7]

Function

Human chorionic gonadotropin interacts with the LHCG receptor of the ovary and promotes the maintenance of the corpus luteum during the beginning of pregnancy. This allows the corpus luteum to secrete the hormone progesterone during the first trimester. Progesterone enriches the uterus with a thick lining of blood vessels and capillaries so that it can sustain the growing fetus. Due to its highly negative charge, hCG may repel the immune cells of the mother, protecting the fetus during the first trimester. It has also been hypothesized that hCG may be a placental link for the development of local maternal immunotolerance. For example, hCG-treated endometrial cells induce an increase in T cell apoptosis (dissolution of T cells). These results suggest that hCG may be a link in the development of peritrophoblastic immune tolerance, and may facilitate the trophoblast invasion, which is known to expedite fetal
development in the endometrium. It has also been suggested that hCG levels are linked to the severity of morning sickness or Hyperemesis gravidarum in pregnant women.

Because of its similarity to LH, hCG can also be used clinically to induce ovulation in the ovaries as well as testosterone production in the testes. As the most abundant biological source is women who are presently pregnant, some organizations collect urine from pregnant women to extract hCG for use in fertility treatment.

Human chorionic gonadotropin also plays a role in cellular differentiation/proliferation and may activate apoptosis.

Production

Like other gonadotropins, it can be extracted from the urine of pregnant women or extracted from cultures of genetically modified microbes with recombinant DNA.

In Pregnyl, Follutein, Profasi, Choragon and Novarel, it is extracted from the urine of a pregnant mare. In Ovidrel, it is protein expressed by microbes with recombinant DNA.

Naturally, it is produced in the placenta by the syncytiotrophoblast.

hCG forms

Total hCG, C-terminal peptide total hCG, intact hCG, free β-subunit hCG, β-core fragment hCG, hyperglycosylated hCG, nicked hCG, alpha hCG, pituitary hCG.

Testing

Blood or urine tests measure hCG. These can be pregnancy tests. hCG-positive indicates an implanted blastocyst and mammalian embryogenesis. These can be done to diagnose and monitor germ cell tumors and gestational trophoblastic diseases.

Concentrations are commonly reported in thousandth international units per milliliter (mIU/ml). The international unit of hCG was originally established in 1938 and has been redefined in 1964 and in 1980. At the present time, 1 international unit is equal to approximately $2.35 \times 10^{-12}$ moles, or about $6 \times 10^{-8}$ grams.
Methodology

Most tests employ a monoclonal antibody, which is specific to the $\beta$-subunit of hCG ($\beta$-hCG). This procedure is employed to ensure that tests do not make false positives by confusing hCG with LH and FSH. (The latter two are always present at varying levels in the body, whereas the presence of hCG almost always indicates pregnancy.)

Many hCG immunoassays are based on the sandwich principle, which uses antibodies to hCG labeled with an enzyme or a conventional or luminescent dye. Pregnancy urine dipstick tests are based on the lateral flow technique.

- The urine test may be a chromatographic immunoassay or any of several other test formats, home-, physician's office-, or laboratory-based. Published detection thresholds range from 20 to 100 mIU/ml, depending on the brand of test. Early in pregnancy, more accurate results may be obtained by using the first urine of the morning (when hCG levels are highest). When the urine is dilute (specific gravity less than 1.015), the hCG concentration may not be representative of the blood concentration, and the test may be falsely negative.

- The serum test, using 2-4 mL of venous blood, is typically a chemiluminescent or fluorimetric immunoassay that can detect $\beta$hCG levels as low as 5 mIU/ml and allows quantification of the $\beta$hCG concentration.

Reference levels in normal pregnancy

The following is a list of serum hCG levels. ($LMP$ is the last menstrual period dated from the first day of your last period.) The levels grow exponentially after conception and implantation.

<table>
<thead>
<tr>
<th>weeks since LMP</th>
<th>mIU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5 – 50</td>
</tr>
<tr>
<td>4</td>
<td>5 – 426</td>
</tr>
<tr>
<td>5</td>
<td>18 – 7,340</td>
</tr>
<tr>
<td>6</td>
<td>1,080 – 56,500</td>
</tr>
<tr>
<td>7 – 8</td>
<td>7,650 – 229,000</td>
</tr>
<tr>
<td>9 – 12</td>
<td>25,700 – 288,000</td>
</tr>
<tr>
<td>13 – 16</td>
<td>13,300 – 254,000</td>
</tr>
<tr>
<td>17 – 24</td>
<td>4,060 – 165,400</td>
</tr>
<tr>
<td>25 – 40</td>
<td>3,640 – 117,000</td>
</tr>
</tbody>
</table>
Interpretation

The ability to quantitate the βhCG level is useful in the monitoring of germ cell and trophoblastic tumors, follow-up care after miscarriage, and in diagnosis of and follow-up care after treatment of ectopic pregnancy. The lack of a visible fetus on vaginal ultrasound after the βhCG levels have reached 1500 mIU/ml is strongly indicative of an ectopic pregnancy. Still, even an hCG over 2000 IU/l does not necessarily exclude the presence of a viable intrauterine pregnancy in such cases.

As pregnancy tests, quantitative blood tests and the most sensitive urine tests usually detect hCG between 6 and 12 days after ovulation.\(^1\) However, it must be taken into account that total hCG levels may vary in a very wide range within the first 4 weeks of gestation, leading to false results during this period. A rise of 35% over 48 hours is proposed as the minimal rise consistent with a viable intrauterine pregnancy.

Gestational trophoblastic disease like hydatidiform moles ("molar pregnancy") or choriocarcinoma may produce high levels of βhCG (due to the presence of syncytiotrophoblasts- part of the villi that make up the placenta) despite the absence of an embryo. This, as well as several other conditions, can lead to elevated hCG readings in the absence of pregnancy.

hCG levels are also a component of the triple test, a screening test for certain fetal chromosomal abnormalities/birth defects.

Uses

Tumor marker

Human chorionic gonadotropin can be used as a tumor marker, as its β subunit is secreted by some cancers including seminoma, choriocarcinoma, germ cell tumors, hydatidiform mole formation, teratoma with elements of choriocarcinoma, and islet cell tumor. For this reason a positive result in males can be a test for testicular cancer. The normal range for men is between 0-5 mIU/mL. Combined with alpha-fetoprotein, β-HCG is an excellent tumor marker for the monitoring of germ cell tumors.\(^{[citation needed]}\)

Fertility

Human chorionic gonadotropin
Human chorionic gonadotropin is extensively used parenterally for final maturation induction in lieu of luteinizing hormone. In the presence of one or more mature ovarian follicles, ovulation can be triggered by the administration of HCG. As ovulation will happen between 38 and 40 hours after a single HCG injection, procedures can be scheduled to take advantage of this time sequence, such as intrauterine insemination or sexual intercourse. Also, patients that undergo IVF, in general, receive HCG to trigger the ovulation process, but have an oocyte retrieval performed at about 34 to 36 hours after injection by, a few hours before the eggs actually would be released from the ovary.

As HCG supports the corpus luteum, administration of HCG is used in certain circumstances to enhance the production of progesterone.

In the male, HCG injections are used to stimulate the Leydig cells to synthesize testosterone. The intratesticular testosterone is necessary for spermatogenesis from the sertoli cells. Typical uses for HCG in men include hypogonadism and fertility treatment.

During first few months of pregnancy, the transmission of HIV-1 from woman to fetus is extremely rare. It has been suggested that this is due to the high concentration of HCG, and that the beta-subunit of this protein is active against HIV-1.

**HCG Pregnyl Warnings**

In the case of female patients who want to be treated with HCG Pregnyl: a) Since infertile female patients who undergo medically assisted reproduction (especially those who need in vitro fertilization), are known to often be suffering from tubal abnormalities, after a treatment with this drug they might experience many more ectopic pregnancies. This is why early ultrasound confirmation at the beginning of a pregnancy (to see whether the pregnancy is intrauterine or not) is crucial. - Pregnancies that have occurred after a treatment with this medicine are submitted to a higher risk of multiplets. - Female patients who have thrombosis, severe obesity or thrombophilia should not be prescribed this medicine as they have a higher risk of arterial or venous thromboembolic events after or during a treatment with HCG Pregnyl. b) Female patients who have been treated with this medicine are usually more prone to pregnancy losses.
In the case of male patients: A prolonged treatment with HCG Pregnyl is known to regularly lead to increased production of androgen. Therefore: Patients who are suffering from overt or latent cardiac failure, hypertension, renal dysfunction, migraines or epilepsy might not be allowed to start using this medicine or may require a lower dose of HCG Pregnyl. Also this medicine should be used with extreme caution in the treatment of prepubescent teenagers in order to reduce the risk of precocious sexual development or premature epiphyseal closure. This type of patients' skeletal maturation should be closely and regularly monitored.

Both male and female patients who have the following medical conditions must not start a treatment with HCG Pregnyl: (1) Hypersensitivity to this medicine or to any of its main ingredients. (2) Known or possible androgen-dependent tumors for example male breast carcinoma or prostatic carcinoma.

**Anabolic steroid adjunct**

In the world of performance-enhancing drugs, HCG is increasingly used in combination with various anabolic androgenic steroid (AAS) cycles. As a result, HCG is included in some sports' illegal drug lists.

When exogenous AAS are put into the male body, natural negative-feedback loops cause the body to shut down its own production of testosterone via shutdown of the hypothalamic-pituitary-gonadal axis (HPGA). This causes testicular atrophy, among other things. HCG is commonly used during and after steroid cycles to maintain and restore testicular size as well as normal testosterone production.

High levels of AASs, that mimic the body's natural testosterone, trigger the hypothalamus to shut down its production of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Without GnRH, the pituitary gland stops releasing luteinizing hormone (LH). LH normally travels from the pituitary via the blood stream to the testes, where it triggers the production and release of testosterone. Without LH, the testes shut down their production of testosterone. In males, HCG helps restore and maintain testosterone production in the testes by mimicking LH and triggering the production and release of testosterone.

If HCG is used for too long and in too high a dose, the resulting rise in natural testosterone would eventually inhibit its own production via negative feedback on the hypothalamus and pituitary gland.

Professional athletes who have tested positive for HCG have been temporarily banned from their sport, including a 50-game ban from MLB for Manny Ramirez in 2009 and a 4-game ban from the NFL for Brian Cushing for a
positive urine test for HCG Mixed Martial Arts fighter Dennis Siver was fined $19,800 and suspended 9 months for being tested positive after his bout at UFC 168. [33]

"HCG Diet"

British endocrinologist Albert T. W. Simeons proposed HCG as an adjunct to an ultra-low-calorie weight-loss diet (less than 500 calories). Simeons, while studying pregnant women in India on a calorie-deficient diet, and "fat boys" with pituitary problems (Fröhlich's syndrome) treated with low-dose HCG, claimed that both lost fat rather than lean (muscle) tissue. He reasoned that HCG must be programming the hypothalamus to do this in the former cases in order to protect the developing fetus by promoting mobilization and consumption of abnormal, excessive adipose deposits. Simeons in 1954 published a book entitled Pounds and Inches, designed to combat obesity. Simeons, practicing at Salvator Mundi International Hospital in Rome, Italy, recommended low-dose daily HCG injections (125 IU) in combination with a customized ultra-low-calorie (500 cal/day, high-protein, low-carbohydrate/fat) diet, which was supposed to result in a loss of adipose tissue without loss of lean tissue. [34]

Simeons' results were not reproduced by other researchers and in 1976 in response to complaints the FDA required Simeons and others to include the following disclaimer on all advertisements:[35]

These weight reduction treatments include the injection of HCG, a drug which has not been approved by the Food and Drug Administration as safe and effective in the treatment of obesity or weight control. There is no substantial evidence that HCG increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or "normal" distribution of fat, or that it decreases the hunger and discomfort associated with calorie-restrictive diets.

— 1976 FDA-mandated disclaimer for HCG diet advertisements

There was a resurgence of interest in the "HCG diet" following promotion by Kevin Trudeau who was later banned from making HCG diet weight-loss claims by the U.S. Federal Trade Commission. [36]

Review studies refuting the HCG diet have been published in the Journal of the American Medical Association and the American Journal of Clinical Nutrition,[37] both concluding that HCG is neither safe nor effective as a weight-loss aid. [38]
A meta analysis found that studies supporting HCG for weight loss were of poor methodological quality and concluded that "there is no scientific evidence that HCG is effective in the treatment of obesity; it does not bring about weight-loss or fat-redistribution, nor does it reduce hunger or induce a feeling of well-being". [39]

There is no scientific evidence that HCG is effective in the treatment of obesity. The meta-analysis found insufficient evidence supporting the claims that HCG is effective in altering fat-distribution, hunger reduction or in inducing a feeling of well-being. The authors stated “…the use of HCG should be regarded as an inappropriate therapy for weight reduction…” In the authors opinion, “Pharmacists and physicians should be alert on the use of HCG for Simeons therapy. The results of this meta-analysis support a firm standpoint against this improper indication. Restraints on physicians practicing this therapy can be based on our findings.”


According to the American Society of Bariatric Physicians, no new clinical trials have been published since the definitive 1995 meta-analysis. [40]

The scientific consensus is that any weight loss reported by individuals on an "HCG diet" may be attributed entirely to the fact that such diets prescribe calorie intake of between 500 and 1,000 calories per day, substantially below recommended levels for an adult, to the point that this may risk health effects associated with malnutrition. [41]

**Homeopathic HCG for weight control**

Controversy about, and shortages[42] of, injected HCG for weight loss have led to substantial Internet promotion of "homeopathic HCG" for weight control. The ingredients in these products are often obscure, but if prepared from true HCG via homeopathic dilution, they contain either no HCG at all or only trace amounts. Moreover, it is highly unlikely that oral HCG is bioavailable due to the fact that digestive protease enzymes and hepatic metabolism renders peptide-based molecules (such as insulin and human growth hormone) biologically inert. HCG can likely only enter the bloodstream through injection.

The United States Food and Drug Administration has stated that over-the-counter products containing HCG are fraudulent and ineffective for weight loss. They are also not protected as homeopathic drugs and have been deemed illegal substances. [43][44] HCG itself is classified as a prescription drug in the United States and it has not been approved for over-the-counter sales by the FDA as a
weight loss product or for any other purposes, and therefore neither HCG in its pure form nor any preparations containing HCG may be sold legally in the country except by prescription. In December 2011, FDA and FTC started to take actions to pull unapproved HCG products from the market. In the aftermath, some suppliers started to switch to "hormone-free" versions of their weight loss products, where the hormone is replaced with an unproven mixture of free amino acids or where radionics is used to transfer the "energy" to the final product.