What is the evidence regarding the public health implications of Human Chorionic Gonadotropin production?

A Rapid Evidence Review

[March, 2023]

Summary

- Gonadotropin therapy is critical for the treatment of infertility by inducing ovulation.
- It can be human-derived from the urine of pregnant women (hCG) (still popular in developing countries) or produced synthetically utilizing recombinant DNA technology (dominates developed countries' market)
- Experiences from different companies shows that, with the exportation of crude hCG comes the issue of re-introducing and availing the finished products to the original country at an affordable cost to the majority of population.
- HCG companies have history of bringing foreign exchange earnings and creating new employment opportunities.
- Although this review did not find reports on the environmental health and ethical issues related to HCG production, the national ethical guidelines, infection prevention and control (IPC) and environmental regulations should be considered for further investigation in the planting of this industry in Ethiopia.
- Administration of human chorionic gonadotropin (hCG) or luteinizing hormone (LH) in male athlete is considered as doping because it increases muscle strength in male. r
- Human chorionic gonadotropin (HCG) is not effective in weight loss and obesity control although it is advertised as if it can serve for this purpose.

What is Rapid evidence Review?

Rapid evidence review addresses the needs of policymakers and managers for research evidence that has been appraised and contextualized to a specific context in a matter of hours or days. This rapid evidence review goes beyond research evidence and integrates multiple types and levels of evidence

For whom is this Rapid Evidence Review for?

This document was created in response to the request made by the Ethiopian Investment Comission. It aims to provide the best available evidence to inform the Ethiopian Investment Comission.

+ Included:

- **Key findings** from the available studies and guidlines

✗ Not included:

- Recommendations
- Detailed descriptions

Background

Human chorionic gonadotropin (hCG) is a glycoprotein hormone which is produced in large amounts during pregnancy and also by certain types of tumour. The biological action of hCG is identical to that of luteinizing hormone, although the former has a much longer plasma half-life. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and thyroid stimulating hormone (TSH) are categorized under one of the three family of HCG (glycoprotein hormone family). The other family are the cystine-knot growth factor family and the therapeutic glycoproteins family. (Barkai et al., 1991).

Follicle stimulating hormone is a member of the glycoprotein hormone family that has a central and essential role in reproduction. Follicle stimulating hormone determination is fundamental to elucidating reproductive physiology, regulating fertility, and diagnosing and treating disorders of reproduction. Follicle stimulating hormone exists in many different molecular forms, which may have different reactivates both in physiological systems and in different assay types (Rose, Gaines Das and Balen, 2000).

How the Issue Came into Attention?

The review was initiated by the Ethiopian Investment Commission where Shuyang Fuxing Biotechnology CO. Limited, a Chinese Company, requested the commission for investment on production of Crude FSH and HCG from urine of pregnant and post-menopausal women. A cooperation letter was written to the Ethiopian Public Health Institute (EPHI) to provide scientific advice on the issue. The letter was forwarded to the Knowledge Translation Directorate to review and synthesize evidence on the topic.

Aim of the Review

The aim of this review is to review and synthesize the best available evidence on public health implication of the production of Crude FSH and HCG from Urine of pregnant and post-menopausal women.

Human Chorionic Gonadotropin for Treatment of Infertility

The use of gonadotropin therapy is critical for the treatment of infertility. In the 1960s, gonadotropin therapy was used to induce ovulation in an ovulatory women, and in the 1980s, it was used to encourage multi-follicular growth in ovulatory women. Chorionic gonadotropin is used to promote the final stages of follicular maturation. Chorionic gonadotropin can be human-derived from the urine of pregnant women (hCG) or produced synthetically utilizing recombinant DNA technology. Urine from postmenopausal women is used to make human menopausal gonadotropin (hMG), also known as menotropin (American Society for Reproductive Medicine, 2008). But it cannot be used in the treatment of threatened miscarriage (Devaseelan, Fogarty and Regan, 2008).

The outcome of infertility treatment with HCG is almost similar with other interventions that serve similar purpose. A review which included 15 trials, covering 2387 women reported little or no difference between urinary-derived gonadotrophins and recombinant FSH in terms of the live birth, multiple pregnancy, clinical pregnancy, or miscarriage rate (Craciunas, Tsampras and Coomarasamy, 2016; Weiss *et al.*, 2019). Gonadotrophins treatment produced more live births without raising the rate of multiple pregnancies in comparison to ongoing clomiphene citrate therapy. Gonadotrophins caused more clinical pregnancies but also more miscarriages than clomiphene citrate (Weiss *et al.*, 2019).

A review that included 18 studies involving 2952 women undergoing in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), reported no evidence of a difference between recombinant human chorionic gonadotrophin (rhCG) or recombinant human luteinising hormone (rhLH) and urinary human chorionic gonadotrophin (uhCG) in the incidence of ovarian hyperstimulation syndrome (OHSS), miscarriage rates, live birth or ongoing pregnancy rates. But it was found that rhCG was associated with a lower number of adverse events (most commonly injection-site reactions) than uhCG (M *et al.*, 2012; Youssef, Abou-Setta and Lam, 2016). Mochtar MH et al. also reported similar findings in their review (Mochtar *et al.*, 2017).

How was this evidence Review prepared?

A rapid evidence synthesis approach adapted from the SURE Rapid Response Service was applied to search and summarize the best available evidence on public health implication of the production Human chorionic gonadotropin (hCG) or Follicle stimulating hormone (FSH). To answer the questions under review the authors of this review searched for relevant studies from databases including the Cochrane Library, Cochrane Menstrual Disorders and Subfertility Group Trials Register, the Cochrane Central Register of Controlled Trials. To include all papers published on Human chorionic gonadotropin (hCG) or Follicle stimulating hormone (FSH), we searched articles using the word “Follicle stimulating Hormone (FSH), Human Chorionic gonadotropin, Hormone, HCG and Urine”. We have also included different studies that are judged relevant for the topic. The searching method and searching words were used flexibility because of the nature of the question and evidence availability.

Other databases were also consulted for this review. These databases includes, Pubmed, Google scholar and Google search.

Abuses Related to Human Chorionic Gonadotropin

Males' testosterone synthesis is stimulated by the parenteral administration of human chorionic gonadotropin (hCG) or luteinizing hormone (LH), and these gonadotropins can therefore be used by athletes to increase muscle strength, to stimulate testosterone production before competition and/or to prevent testicular shutdown, which is seen as doping in sport (Barkai *et al.*, 1991; Stenman,

Hotakainen and Alfthan, 2008; Handelsman, 2015). So, the administration of hCG and Luteinizing Hormone (LH) was banned by the International Olympic Committee (IOC) and International Convention Against Doping in Sport (Commonwealth, 2010). Women's hCG levels have not been shown to increase muscle strength, while pregnancy is a common source of elevated hCG levels in females. The use of gonadotropins is therefore prohibited only in males but not in females. Because urine is utilized for doping control, all commercially available hCG tests have been designed to determine hCG in serum rather than in urine (Stenman, Hotakainen and Alfthan, 2008).

In some cases, HCG is advertised as if it can be used for weight loss and obesity control. But studies are reporting against this assumption. A meta-analysis involving 24 studies found that there is no scientific proof that HCG works to cure obesity; it does not cause weight loss or fat redistribution, nor does it lessen hunger or make one feel well (Lijesen *et al.*, 1995).

Lesson from Organon India

By forming alliances with different companies, Organon, a hormone companies, was established in the Netherlands in 1923. After the 1960s, Organon established affiliates all over the world to market its goods. Moreover, it expanded its quest for raw materials internationally, opening a unit in Kolkata, India, in 1961. Organon opened two production facilities in Kolkata at the beginning of the 1970s: one for pharmaceutical products and one for bulk medications. The business requested an industrial license from the Indian government in 1974 in order to produce steroids and export hCG (Bärnreuther, 2018).

Upon the receipt of the permits, Organon India started to extract hCG from the urine of pregnant women in India. Starting from 1975, crud hCG was shipped to the Netherlands. This signifies that neither the formulation production nor the full purification of the exported chemical occurred in India. The branded medication was ultimately manufactured and purified in the Netherlands. Furthermore, the finished product was only introduced in ampoules to India after ten years and they were too expensive for the local people (Bärnreuther, 2018).

The good news is that the company was successful in bringing foreign exchange earnings and created new employment opportunities in India. But in the late 1980s, a new generation of fertility medications had been introduced. Recombinant hCG was praised in the medical community for its purity since it promised less biological contamination and higher levels of consistency in quality. It is produced using biotechnology and no longer requires urine as a raw material. So, hCG production unit in Kolkata was shut down in the beginning of the 1990s (Bärnreuther, 2018).

Although these modern, recombinant forms currently dominate the global market, highly purified urinary products remain popular, especially in developing nations. Pharmaceutical companies in India still continue to produce urinary products utilizing Chinese-imported crude hCG (Bärnreuther, 2018).

Public health considerations

The major body of evidence is concentrated on clinical activity and efficacy of FSH and LH. Thus, this review shows the public health considerations based on the few studies available and authors' expertise.

- Possible impact on the environment, ethical issues related with involvement of human subjects in sample provision, occupational hazards and safety are public health issues that need focus during planting the industry.
- In relation to sample collection, since urine is a bio data its management should be in a way that doesn't harm the environment, community, and individual clients. This can be looked at closely by specific regulatory bodies in the country.
- Infection prevention and control (IPC) approaches need to be based on the World Health Organization (WHO) guideline and the ministry of health protocols.
- Although authors have not found direct reports on public health considerations related to HCG & LH production, the national rules and regulations on ethical consideration, Infection Prevention and Control (IPC), environmental health and occupational hazard should be followed.
- Matters and ethical dilemmas arising from such practices must be settled by the NERC (National ethical review committee)

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Conflict of interest

- There is no conflict of interest to declare.

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