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REVIEW

Evidence for, and Associated Risks with, the Human Chorionic Gonadotropin Supplemented Diet

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ABSTRACT. Trend diets can be commonplace amongst those who are trying to lose weight but in most cases there is some shred of evidence to suggest they might be of some benefit. Seldom is there a diet which is such a fad that it is not only completely unfounded but also potential harmful. The human chorionic gonadotropin or "hCG diet" is such a diet, which after half a century still has no evidence to support its efficacy; in fact all scientific publications subsequent to the original article counter these claims. In this short communication, we review the literature and present data on exactly what some of the hCG diet preparations actually contain and highlight that, based on current data, these may do more harm than good. It is worrying that more consideration is not given to the possible danger of administration of hCG preparations to individuals without an evidence-based rational.

Over half a century ago, an article was published in the general medical journal, The Lancet, which claimed human chorionic gonadotropin (hCG) was an incredible diet supplement that promoted fat mobilization and weight loss (Simeons, 1954). Unfortunately, the article used methodologies that were poorly controlled, and all subsequent studies have refuted the claims. However, as a result of that article, the "hCG Diet" is advertised today on hundreds of internet websites, which both sell hCG and promote weight loss clinics that prescribe this supplement. As a consequence of the original article and its increased popular following, the diet has become the main global use of therapeutic hCG. At the same time, we are revealing increasing evidence that certain forms of hCG promote cancer growth, and we are developing anticancer vaccines and therapies that target hCG as an adjuvant therapy in cancer management.

hCG is generally believed to be a harmless hormone, which is produced during pregnancy and can be detected in the maternal urine. It also has been shown that exogenous hCG was a good promoter of endogenous testosterone and anabolism in men (Landau, Knowlton, Lugibihl, Brandt, Kenyon, 1950). Thus, hCG has become

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a drug abused by athletes, sportsmen, and body builders (Delbeke, 1996; Kicman & Gower 2003; Kochakian, 1990; Tricker, O'Neill, Cook, 1989); therefore, hCG is currently on the World Anti-Doping Programme list of banned substances in sports (http://www.wada-ama.org). Today, it appears that the most widespread use of therapeutic hCG is for diet, the second as an anabolic steroid, and the third major use is the legitimate evidence-based application in assisted reproduction for the induction of ovulation.

The legitimate requirement in fertility treatments led to the development and production of a wide assortment of therapeutic grade hCG preparations (some of which are detailed in Table 1). In addition to these, the "hCG Diet" has led to the availability of some very crude urinary hCG preparations, along with degraded hCG preparations, and falsely marketed preparations, which have very little or no hCG in them. These lower grade preparations are now sold mostly by internet sites advertising dietary or anabolic applications. Generally, preparations can be administered by intramuscular or subcutaneous methods, or by the rather questionable nasal or oral administration; it is worth noting that no hCG has ever been demonstrated to absorb this way.

In the original Lancet article on hCG and diet, studies were conducted in which participants were restricted to 500 Kcal per day and were given 125 IU (~12.5 ng or 450 nmol) urinary hCG as a supplement; weight loss results were reported (Simeons, 1954). The weight loss described was attributed to the vague and unexplained fat-mobilizing effects of the hCG injections, which were also claimed to suppress appetite. Just five years later, in 1959, a second study contradicted the earlier findings and suggested that the claims of this diet were false (Sohar, 1959). This second study suggested that the weight loss was solely due to the 500 Kcal diet and not the hCG supplementation. Subsequently, in the 1960s, Craig et al. (1963) and Frank (1964) each conducted their own studies based on the initial diet. Independently, both studies came to the same conclusion that there was no possible relationship between hCG administration and loss of weight or hunger suppression. More recently, double blind studies have failed to confirm any evidence that hCG has any role as a dietary supplement, that it can mobilize fat, or is an appetite suppressant of any kind (Bosch, Venter, Stewart, Bertram, 1990; Richer & Runnebaum, 1987; Shetty & Kalkoff, 1977; Stein, Julis, Peck, Hinshaw, Sawicki, Deller, 1976; Young, Fuchs, Woinjen, 1976). In 1995, a meta-analysis of 14 random controlled studies and 10 nonrandom controlled studies concluded "there is no scientific evidence that hCG causes weight loss, a redistribution of fat, staves off hunger, or induces a feeling of well-being" (Lijesen, Theeuwen, Assendelft Van Der Wal, 1995). As such, we feel that an "hCG diet" is a misnomer, considered both inappropriate and unethical, with the bulk of evidence widely ignored by the public and some practitioners.

Today, we have a much better understanding of hCG biology than we did in the 1950s and second half of the last century (Cole & Butler, 2014). It is now well established that many structural variants of hCG exist in urinary and recombinant hCG preparations. Most concerns of these variants are hyperglycosylated hCG (hCGh) and hCG free β-subunit (hCGβ), which have been shown to directly promote the growth and spread of cancer (Cole & Butler, 2014). In the 1970s and 1980s, hCGβ

TABLE 1. Examples of hCG variant distribution in common pharmaceutical hCG preparations

Preparation	Origin	IntacthCG, undamaged, with normal glycosylation	Hyperglycosylated hCG	Nicked hCG	hCG free β-subunit	hCG β-core fragment	Biological activity calibrated with WHO third I.S. (IU/mg)
SeronoOvidrel	CHO cell recombinant	100%	<0.1%	<0.1%	<0.1%	<0.1%	11,900
SeronoProfasi	Pregnancy urine	92%	6.0%	<0.1%	1.6%	0.6%	10,000
Scripps >99% hCG	Pregnancy urine	82%	2.2%	14%	0.8%	0.8%	11,000
Scripps >80% hCG	Pregnancy urine	57%	6.8%	15%	5%	16%	9,000
FerringChoragon	Pregnancy urine	40%	4%	12%	5%	39%	5,000
OrganonPregnyl	Pregnancy urine	31%	7%	10%	12%	40%	3,000
Scripps >15% hCG	Pregnancy urine	11%	13%	13%	13%	50%	2,000
Sigma C5297	Pregnancy urine	8%	12%	14%	14%	52%	3,000

Note: Contents of free subunits and fragments in common pharmaceutical preparations of hCG were compared with intact hCG on a molar basis. Percentages are molar percentages of total hCG immunoreactivity. Products are sorted in order of descending proportions of intact (normal) hCG.

production was identified in many cancer cell lines, and in serum and urine of numerous cancer patients. At that time, hCGβ production was considered incidental and not more than a bystander effect of the metastatic process. However, over the last couple of decades, hCGβ and more recently hCGh have been shown play a direct role in the growth, metastasis, and resistance to therapy in many cancers that produce them. The hCG molecules produced in cancer appear to act as autocrine growth factors, antagonizing apoptosis, and directly promoting metastasis, whereas hCG (the pregnancy hormone itself) appears to have no cancer promoting effect (Cole & Butler, 2014).

Pharmaceutical hCG preparations vary widely in purity and content of hCG and hCG variants (Table 1). In some cases, gallons of pregnancy urine from anonymous sources are concentrated for extraction, or partial extraction, of hCG by organic precipitation and chromatography. All purified hCG preparations contain an array of very similar molecules with identical amino acid sequences, making them virtually inseparable and indistinguishable in heterogeneous mixtures derived from urinary sources. Therefore, hCGh and hCGβ, which are both produced in pregnancy, are found in most therapeutic preparations. Urinary hCG preparations contain between 2.2% and 16% hCGh and contain between 0.8% and 14% hCGβ (Table 1). Taking hCGh and hCGβ together, 3.0%–26% of the hCG product in urinary pharmaceutical preparations may be a variant of hCG associated with cancer, resistance to therapy, metastasis, and poor prognosis. hCGβ core fragment (hCGβ cf) has not been studied extensively as a cancer promoter but accounts for 0.8%–52% of the hCG-related molecules in urines. Considering hCGβ cf, in addition to others, a total of 3.8%–78% of the urinary preparations sold as hCG may actually be comprised more of hCG variant or hCG degradation product than hormonal hCG. Therefore, all hCG preparations by nature contain fragments of hCG from metabolic dissociation and degradation; the only exception was believed to be the recombinant hCG preparation. However, more recent studies have shown that when recombinant hCG is administered, hCGβ and hCGβ cf can still be detected in patient serum and urine (Norman, Buchholz, Somogyi, Amato, 2000). Many dietary hCG supplements now also have been made as nasal drop and pill preparations, and we were surprised, perhaps relieved, to find very little or no immunologically active hCG present in many of these samples. Furthemore, we question if any active component would find its way into the circulation when administered by this route. These preparations may contain no hCG at all, are therefore not hCG, and are therefore not described in Table 1.

It is worrying that more consideration is not given to the possible danger of administration of hCG preparations potentially containing hCGh and hCGβ to individuals without an evidence-based rational. These hCG forms may initiate precancer cells, promoting growth and invasion in cells that may otherwise be suppressed or lie dormant (Cole & Butler, 2012). It is specifically these forms of hCG, rather than the hormone, which exhibit these effects, and anticancer vaccines have even been developed to target these molecules (Butler, Staite, Iles, 2003; Cole & Butler, 2008; Iles, Delves, Butler, 2010; Morse et al., 2011). Perhaps most worryingly, anecdotal cases and internet threads are now emerging linking cancer cases and disease recurrence with those taking hCG supplements as a diet aid and more recently with a case of DVT and pulmonary embolism that was attributed to an hCG

supplemented diet (Goodbar, Foushee, Eagerton, Haynes, Johnson, 2013). Until more information is available on long term effects of hCG supplementation, we recommend that the use of hCG preparations outside evidence-based applications need to be more tightly controlled, and that doses used in assisted reproduction, which are often needlessly high (Butler, 2003), should be more carefully considered especially in those with a previous history of cancer.

Declaration of Interest: The authors declare no conflict of interest relating to the use of hCG or any of its subunits as dietary supplements for the use in weight loss.

ABOUT THE AUTHORS

Stephen Butler is Chief Scientific Officer at MAP Diagnostics and has been working on the structure and function of hCG and hCG subunits for over 20 years. **Laurence Cole** is the Director of the USA hCG Reference Service and has been working on the structure and function of hCG, its variants and subunits for almost 40 years.

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