

Mini Review

Adverse effects on consumer's health caused by hormones administered in cattle

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Abstract

In today's digital age to feed this ever increasing population there is a high demand for more production of food. To meet this task, artificial hormones are being used to increase the production of milk and meat. In this review, we address the controversial issue of adverse effects of hormones being administered in cattle. Oestradiol, Progesterone, Testosterone, Zeranol, Trenbolone and Melengestrol hormones are approved by U.S. food and drug administration (FDA) for commercial use. These have been found to be used to increase the quantity of milk and meat in cattle but their adverse effects being observed on the consumers as they cause cancer and premature puberty in children. Similarly the utilization of recombinant bovine growth hormone (rBGH) in cattle is seen to be a burning issue as it causes cancer. Here, we present a deeper insight to above mentioned content

Keywords

*Recombinant bovine growth hormone,
Milk,
Cattle meat,
Prepuberty,
Insulin like growth factor,
Cancer*

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Introduction

Hormones are chemical messengers produced by glands that are used to communicate between organs and tissues through the circulatory system. The major function of hormones is to regulate physiological and behavioural activities such as digestion, metabolism, respiration, sensory perception, sleep, stress, growth and reproduction (Neave, 2007). Based on their chemical structure hormones are classified into four classes which include (i) Aminoacid derivatives (Thyroxin), (ii) Peptides, polypeptides and proteins (Insulin), (iii) Eicosanoids (Prostaglandins), and (iv) Steroid (Testosterone) (Marieb and Hoehn, 2007). These synthetic hormones are beneficial to human beings, but they also have adverse effects such as prostate, breast and ovarian cancer (Epstein, 1996; Bohlke *et al.*, 1998). In this current review, we deal with the hazards of rBGH in milk and side effects of hormonal residue found in meat.

Recombinant Bovine Growth Hormone (rBGH) belongs to steroid is a transgenic substance injected into dairy cattle to increase milk production. rBGH have potential to increase milk production from 8 to 12 pounds per day for a cattle. The DNA responsible to produce bovine growth hormone in cow is combined with a plasmid vector from E.Coli bacteria. Later, this is allowed to reproduce, enriches the quantity of the

rBGH hormone (Bauman *et al.*, 1985; Elvinger *et al.*, 1988; Monsanto Company, 2003). However, rBGH does not directly cause any side effects, but act as a basis for increased amounts of Insulin-like Growth Factor-1 (IGF-1) hormone. This IGF-1 hormone causes health issues in human beings. Human IGF-1 and bovine IGF-1 are chemically similar and allows bovine hormone to be biologically active in humans (Vermont Public Interest Research Group, 2002). When a biologically active bovine IGF-1 hormone is ingested by humans in higher quantity, it becomes more active and dangerous substance.

The growth hormones Oestradiol, Progesterone, Testosterone (Natural) and Zeranol, Trenbolone, Melengestrol (Synthetic) have a potential risk to human health. These hormones are administered in cattle for growth promotion purposes. The hormone residues in meat results into adverse effect on human health such as disrupt in human hormone balance, causing developmental problems, interfering with the reproductive system and can even lead to the development of breast, prostate or colon cancer (Galbraith, 2002; Ganmaa and Sato, 2005).

rBGH and its mode of action

Bovine Growth Hormone (BGH) is a natural

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occurring protein produced in cows, whereas recombinant Bovine Growth Hormone (rBGH) is a genetically engineered, synthetic version of the hormone. It works through a series of different biological processes in cattle which is not directly responsible for increased milk production, but it stimulates liver that initiates the release of growth hormone IGF-1. This hormone enhances the milk production in cows (Vermont Public Interest Research, 2002). Further, it also found to increase the rate of blood flow through the mammary gland and leading to production of large number of mammary cells. It improves the ability of existing cells to synthesize more milk. Moreover, it also decreases the capability of the body to synthesize fat and making free fatty acids available for milk production. This extends lactation periods for up to three times more than their normal length. This process doubles the metabolic stress on the cow causing lack of essential nutrients such as calcium and phosphorus (Bedford, 2000). It has been reported that application of rBGH (Ex. Recombinant Bovine Somatotropin - rBST) increases the amount of excreted IGF-1 in milk by 25-70% (Prosser *et al.*, 1989; European Commission, 1999).

Effects on human health

The existing research work has been revealed that rBGH does not responsible for human health problems, but it initiates the production of IGF-1 to high levels. Their presence in milk is resistant to pasteurization. Consequently, the consumption of milk from rBST treated dairy cows will increase the daily intake of bovine IGF-1 (Slaba *et al.*, 1993; European Commission, 1999). Human IGF-1 and bovine IGF-1 are chemically similar and allowing the bovine hormone to be biologically active in humans. The role of IGF-1 in cancer is supported by epidemiological studies. It reveals high levels of circulating IGF-1 which is associated with increased risk of several common cancers such as prostate, breast, colon-rectum and lung (Li *et al.*, 1998; Yu and Rohan, 2000; Wei *et al.*, 2015).

Gastrointestinal cancer

The combination of IGF-1 in BST-milk and IGF-1 in the human gastrointestinal lumen would augment intraluminal concentrations of this hormone. This increases the possibility of local mitogenic effects on gut tissues (Mephram *et al.*, 1994).

Breast cancer

In a study of 94 cases of premenopausal ductal carcinoma in situ and 76 controls which indicates

the risk of breast cancer by the association of plasma IGF-1 and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3). Compared with women in the lowest tertile of IGF-1 and upper two tertiles of IGF-1 are the elevated risk factor for ductal carcinoma in situ (Aizu-Yokota *et al.*, 1994).

Prostate cancer

IGF-1 is a mitogen for prostate epithelial cells. To investigate associations between plasma IGF levels and prostate cancer risk, a case-control study within the physicians was conducted on prospectively collected plasma from 152 cases and 152 controls. A strong positive association was observed between IGF-1 levels and prostate cancer risk (Chan *et al.*, 1998).

rBGH has been used for past 50 years. Due to this reason, the incidence of breast cancer in U.S. women was increased to one in eight women from one in 20 (Green, 2002). Both low-calorie diet and low birth weights can protect against breast cancer but also decreases the amounts of IGF-1. A study was conducted showing a seven time increased risk of breast cancer in pre-menopausal woman with high levels of IGF-1 in their blood and a four time increase of prostate cancer in men with high levels of IGF-1 in their blood. rBGH may also be responsible for the cause of decreasing in average age of girls in the United States showing first signs of puberty and menstruation (Green, 2002). Children are also at risk for abnormal development, especially their reproductive and immune systems are still in developing stage. Premature growth stimulation is a real concern with sustained intakes of high levels of IGF-1 (Mephram *et al.*, 1994).

Mastitis and related side effects

Mastitis is an inflammation of the udder of cattle. The risk of mastitis is 25% greater with the use of rBGH with cases being more severe and long-lasting. The health dangers in dairy cattle caused by rBGH can itself cause other serious health issues in humans by consuming their milk. With a higher incidence of infection such as mastitis in cows injected with rBGH, which increased the demand for the use of antibiotics. Many people are allergic to antibiotics and may find themselves in dangerous to consume their milk. Today, antibiotic resistance in bacteria is a growing concern and causing common antibiotic medicines to become useless as bacteria becomes immune to them (Galbraith, 2002; Vermont Public Interest Research Group, 2002).

Risks to human health from hormone residues in cattle meat and meat product

Oestradiol benzoate, Progesterone, Testosterone propionate, Zeranol, Trenbolone acetate, and Melengestrol acetate are used to increase the meat quantity in cattle. Basically these hormone derivatives except melengestrol (MGA) are usually placed alone or in combination with other steroidal hormones in cattle as compressed pellets on their ears but MGA is given orally 0.25-0.5 mg/day (Scientific Committee on Veterinary Measures Relating to Public Health, 1999). Generally the dose contains 8-20 mg of Oestradiol benzoate, 200 mg of Progesterone, 100-200 mg of Trenbolone acetate, 36 mg of Zeranol and 40-300 mg of Trenbolone acetate (Galbraith, 1997; Brandt, 1997). Meat and meat products derived from the cattle have the potential risk to human beings (Galbraith, 2002).

Oestradiol-17 β

Oestradiol-17 β (Figure 1(a)) is the most active female sex hormone secreted by the ovary, the adrenals and the testis. They affect many functions in the organs and systems in humans related to reproductive function. Oestradiol is synthesized and secreted in early stages of embryogenesis and has an active role in the normal development of the female sex accessories during the lifetime of females (Norman and Litwack, 1997).

Progesterone

Progesterone (Figure 1(b)) is a natural steroid sex hormone secreted by the corpus luteum in the ovary of cycling females. Its function in reproduction is linked to the implantation of the egg in the uterus and the growth of the embryo and foetus. As all hormones, progesterone secretion is regulated by a series of positive and negative feedback mechanisms of the brain (hypothalamus, pituitary) (Norman and Litwack, 1997).

Testosterone

Testosterone (Figure 1(c)) and its more active metabolite, dehydrotestosterone are the main sex hormones secreted by males. Testosterone is responsible for the early development, appearance and maintenance of secondary male sex accessory organs (prostate, secretory glands, penis size, etc) during adulthood. Testosterone secretion is also affected by the complex interaction among all endocrine glands, especially with those in the brain. As with the above mentioned sex hormones, testosterone is metabolized and as a result, metabolites of different activity are generated (Norman and Litwack, 1997).

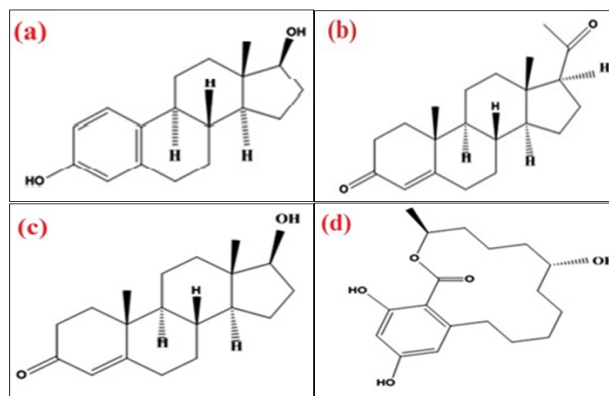


Figure 1. Chemical structures of (a) Oestradiol-17 β hormone, (b) Progesterone hormone, (c) Testosterone hormone and (d) Zeranol hormone

Zeranol

Zeranol (Figure 1(d)) is a natural myco-oestrogen derived from zearalenone produced by different species of Fusarium molds. Animals with natural oestrogen, zeranol affect oestrogen target organs and therefore disturb reproductive patterns when introduced accidentally or intentionally in susceptible hosts (Lindsay, 1985).

Trenbolone

Trenbolone (Figure 2(a)) is a synthetic androgen having anabolic activity, several folds above that of testosterone. Trenbolone is metabolized into 17-trenbolone, a most active derivative (Donner *et al.*, 2015).

Melengestrol

Melengestrol (Figure 2(b)) is a synthetic hormone, about 30 times as active as progesterone. It interferes with the oestrous cycle through the same feedback mechanisms described for progesterone. Its metabolic effect is due to its ability to increase oestrogen levels in treating heifers (Bartelt-Hunt *et al.*, 2012).

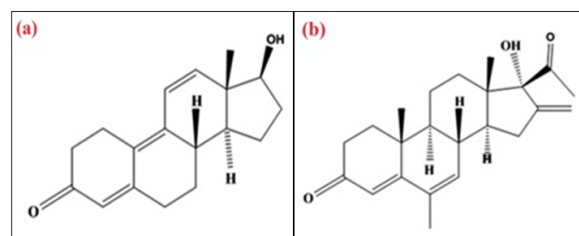


Figure 2. Chemical structures of (a) Trenbolone hormone and (b) Melengestrol hormone

Quantification of hormones in edible tissue

The above mentioned hormones are administered through subcutaneous implants or by mixing in the feed of the cattle. Implants contain either a single

Table 1. Endogenous Steroid Hormone Levels in Females and Males

Hormone	Women (pg/ml)			Men (pg/ml)	
	Pre-pubertal	Follicular-Luteal	Post-menopausal	Pre-pubertal	Adult
Oestradiol	8 to 23	10 to 375	0 to 28	5 to 14	6 to 44
Estrone	19	15 to 250	15 to 55	16	10 to 65
Progesterone	0.1 to 0.4	0.2 to 24	-	0.1 to 0.3	0.3 to 0.5
Testosterone	0.1 to 0.2	0.4 to 0.8	0.4 to 0.8	0.1 to 0.2	3 to 9

Sources: Zeleniuch et al. (2004); Angsusingha et al. (1974); Szymczak et al. (1998); Woolcott et al. (2010); Toniolo et al. (1995); Lippe et al. (1974); Toner et al. (1991)

Table 2. Limits and adverse effects of hormonal growth promoters

S. No.	Name of the Compound	ADI μ g/kg bw*#	Residue in animal's muscle (μ g/kg)	Adverse Effects
1.	17 β - Estradiol	0 to 0.05	0.011 to 0.28	Changes in menstrual cycle
2.	Testosterone	0 to 2	0.23 to 0.77	Androgenic effects
3.	Progesterone	0 to 30	0.031 to 0.360	Changes in the uterus
4.	Zeranol	0 to 0.5	2	Estrogenic effects
5.	Melengestrol acetate	0 to 0.03	1	Changes in menstrual cycle
6.	Trenbolone	0 to 0.02	2	Androgenic effects acetate

represents Acceptable daily intake; * indicate Body weight.

Sources: JECFA (1988); JECFA (2000b); JECFA (2006c); Paris et al. (2006); Jeong et al. (2010)

hormone or in combination to promote growth and enhance the efficiency of food utilization in beef cattle. Thus humans consuming beef from untreated cattle are exposed to residues of oestradiol, testosterone and progesterone and their metabolites which are naturally present in the meat. Zeranol, Trenboloneacetate (TBA) and Melengestrolacetate (MGA) are added to cattle feed and their background level in humans should be zero. Consumption of meat from cattle treated with the above mentioned hormones causes increased exposure to them. The use of growth promoting hormones results in an excess daily intake of oestrogens of 1.1 to 83.9 mg/person, progesterone of 64-467 mg/person and testosterone of 5-189 mg/person. It indicates that these data refer to the parent compounds only and not include contributions from metabolites.

Table 1 show that a sufficient range of hormone's presence in the human body as per previous findings and hospital clinical pathology lab normal ranges. Thus prepubertal, postmenopausal women and prepubertal adult men have the lowest levels of endogenous oestrogens and progesterone. It represents that individual at increased risk for adverse health issues that are associated with exposure to exogenous sources of oestrogen. Women and prepubertal men represent higher risk for adverse health problems that might be associated with exposure to exogenous sources of testosterone. Table 2 highlights the acceptable intake of hormonal

growth promoters, deposited levels in treated animals and their adverse effects.

Deposition of hormones in animal and their biotransformation in human

The six steroidal hormones (Oestradiol benzoate, Progesterone, Testosterone propionate, Zeranol, Trenbolone acetate, and Melengestrol acetate) which are used in cattle to increase quantity of meat have been deposited in the organs of the animal. The deposited hormones are transformed into its derivatives which are biologically active in human beings (Bircher *et al.*, 2015).

Oestradiol

It was found to deposit in muscle, liver, kidney, and fat of animals. After administration of oestradiol benzoate, the major oestrogenic metabolites in human (17 α -oestradiol, 17 α -oestradiol-glucuronide, estradiol and estrone) are transformed into 3- β -D-glucuronate of 17 α - oestradiol, and other 17-glycosides of oestradiol (Sangsritavong, 2002).

The liver is the primary site of oestrogen metabolism, where rates of 2- and 16 α -hydroxylation catalysed by cytochromes P4501A2, P4503A3 and P4503A4 greatly exceed 4-hydroxylation. Extra hepatic tissue causes 4-hydroxylation of oestradiol, which may play a significant role in oestrogen homeostasis (Michnovicz *et al.*, 1986).

Testosterone

It was found to deposit in muscle, liver, kidney and fat of animals. In humans, the oxidative metabolism of testosterone occurs predominately in the liver at the 6 β -position, and to a lesser extent at 15 α -, 15 β , and 2 β -positions. Cytochrome P4503A4 has been shown to be the major testosterone 6 β -hydroxylase in human liver, catalyzing testosterone hydroxylation at the 15 α -, 15 β -, and 2 β -positions, as well. Human liver cytochromes P4502C9 and P4502C19 also have been shown to possess significant testosterone hydroxylase activity (Yamazaki and Shimada, 1997).

Progesterone

An increase in progesterone concentration was estimated in fat tissue of male calves. In humans, the oxidative metabolism of progesterone occurs in the liver at the 6 β -position and to a lesser extent at the 16 α - and 2 β -positions. Cytochrome P4503A4 has been shown to be the major progesterone hydroxylase, catalyzing the formation of each of these products (Michnovicz *et al.*, 1986). Significant extra hepatic metabolism and clearance also has been observed and is believed to precede subsequent to an initial 5 α -reduction via non-cytochrome P450 routes. Absorption of exogenous progesterone in humans is rapid. Only a small fraction of the administered dose is detected as progesterone in serum, while most of the steroid circulates as inactive 5 β -pregnane-3 α -ol-20 α -diol-glucuronide (Adlercreutz and Martin, 1980; Adlercreutz *et al.*, 1994).

Trenbolone acetate (TBA)

TBA is rapidly metabolised to its free active form, alpha and beta Trenbolone hydroxide (TBOH). In cattle, the β -epimer is the major metabolite in muscle. The α - and β -TBOH are deposited in muscle, liver, kidney and fat of treated cattle.

The metabolism of trenbolone in humans has not been extensively studied. The metabolites found were present as glucuronides, which contained mostly 17 α -trenbolone, 17 β -trenbolone and trendione (Bircher *et al.*, 2015). While other polar metabolites, presumably hydroxylated products were detected in lesser amounts.

Zeranol

Zeranol is mainly metabolised in animals to zeralenone and taleranol. Only a few studies were available and discussed by the FAO/WHO. It was concluded that the mean residue levels calculated as zeranol equivalents did not exceed 0.2 μ g/kg in muscle, 10 μ g/kg in liver, 2 μ g/kg in kidney and 0.3 μ g/kg in fat.

In humans, the half-life of zeranol plus and its metabolites in the blood was 22h. Urinary excretion was predominant and included glucuronide and sulfate conjugates. The half-life of zeranol suggests that this compound and its derivatives can accumulate in humans consuming zeranol-containing food on a regular basis (Bircher *et al.*, 2015).

Melengestrol Acetate (MGA)

The highest concentration of MGA and its derivatives was found in the liver of treated cattle, although fat was found to be the actual target tissue for MGA. After withdrawal of the implant within 48 hrs, concentration in fat tissue was seen to decrease.

MGA is extensively metabolized in women to more than 20 compounds, with 74% excreted in urine and faeces. Intact MGA, as well as its glucuronide and sulphate conjugates, were identified in urine. Two of the metabolites have been tentatively identified as the 2 α -hydroxy and 6-hydroxymethyl derivatives (Bircher *et al.*, 2015).

Carcinogenicity, genotoxicity, and DNA damage

The biologically transformed hormone derivatives produce several health issues, including abnormal growth of cells, gene disorder, and forms DNA adducts that leads to DNA damage (Hoffmann, 1981; Metzler and Pfeiffer, 2001; Stepniak and Karbownik-Lewinska, 2016). The natural estrogens can cause various types of DNA damage and permanent genetic changes that may have relevance for carcinogenesis (Liehr, 2000, 2001)

Oestradiol

There is no direct evidence on the consequences of the contribution of exogenous 17 β -oestradiol originating from the consumption of treated meat. Yet from the data derived from human populations, the physiological values of hormones in the blood are within range, high levels are associated with an increased risk of breast cancer (Adlercreutz *et al.*, 1994). The carcinogenic effect of 17 β -oestradiol in animals under observation as well as the deleterious effects in pre- and perinatal development was found. Finally, in consideration of the recent data on the formation of genotoxic metabolites of oestradiol suggesting that 17 β -oestradiol acts as a complete carcinogen by exerting tumour initiating and promoting effects.

Oestradiol is an endogenous oestrogen that undergoes extensive tissue specific oxidative metabolism. The predominant metabolites are the prooxidant 2-OHE and 4-OHE, which can undergo further biotransformation to semiquinones and

quinones. Redox cycling of the semiquinones and quinones can produce superoxide and the quinones can form DNA base adducts. Thus, oestrogen oxidative metabolites can be directly or indirectly genotoxic (Zinedine *et al.*, 2007). In a couple of studies, it has been proven that oestradiol exposure shows MTX resistance which generally arises through gene amplification. If this turns out to be the mechanism of enhancement by the oestrogens, it would support the view that oestrogens have direct, destabilizing effects on the genome (Frenkel, 1992).

Oestradiol is converted in vivo to genotoxic metabolites and also form DNA adducts which damages DNA. Aneuploidy and altered chromosomal structure were observed, which subsequently transformed into tumor cells. Some of the hydroxy and methoxymetabolites of E1 and E2 disrupt cytoplasmic microtubules, abnormal spindle formation, fragmented spindle poles and uneven chromosome distribution (Le Guevel and Pakdel, 2001).

Testosterone

Although endogenous testosterone may play a role in the occurrence of prostate cancer. However, in consideration of the limited data on genotoxicity and testosterone might be aromatized to oestradiol, which had found to be genotoxic (Nussey and Whitehead, 2001).

Progesterone

The evidence is considered sufficient in experimental animals for the carcinogenicity of medroxy progesterone acetate, (inadequate for levorgestrel). Progestogen only in the form of contraceptives is possibly carcinogenic to humans (Nussey and Whitehead, 2001).

Trenbolone acetate (TBA)

It has to be noted that a considerable fraction of TBOH residues seems to be covalently bound to the tissues. Formation of DNA adducts was observed in rat hepatocytes cultured with 30mM β -TBOH (Schiffmann *et al.*, 1985).

Zeranol

Dose-dependent induction of adenomas and carcinomas of the liver were found in zeranol-treated male and female Armenian hamsters, reaching 100% for adenomas and 75% for carcinomas at the highest dose (Coe *et al.*, 1982). In comparison with DES, zeranol was much more carcinogenic to the liver than expected based on its relative oestrogenic activity.

DNA adducts of zeralenone (of which zeranol is

a metabolite) have been observed in the kidney and liver of female mice treated with a single dose of zearalenone (2mg/kg) (Baldwin *et al.*, 1983). After repeated doses of zearalenone, DNA adducts were recovered in mouse ovaries. Complete inhibition of DNA synthesis was produced in human peripheral blood lymphocyte cultures at a concentration of 30 μ g/mL.

Melengestrol acetate (MGA)

The lack of data on mutagenicity/carcinogenicity and on DNA interactions and in consideration of carcinogenicity studies conducted only in one animal species. Previous findings reveal that it stimulates tumour formation in mammary glands (McAloose *et al.*, 2007).

Effects on growth and reproduction

Oestradiol, Progesterone, Testosterone, Zeranol, Trenbolone, and Melengestrol are the hormones that are responsible for the secondary sexual growth in men and women. So the derivatives of these hormones affect the growth and fertility (Galbraith, 2002).

Oestradiol

Here observations strongly suggest that environmental 17 β -oestradiol can modulate the growth of children and decrease the age even puberty is reached. 17 β -oestradiol exerts a feminizing effect on secondary sexual characters. During adolescence, the increasing serum level of oestradiol induces breast and uterus development in girls. In boys with a dominant mutation leading to an aromatase excess, enhanced oestradiol levels in plasma are associated with heterosexual precocity and breast development (gynecomastia) (Partsch and Sippell, 2001). It has been noticed that in men, infertility has been associated with an increase in intratesticular aromatase, leading to increase in intratesticular and seminal oestradiol levels (Endo-Ichikawa *et al.*, 1995).

Testosterone

In adolescent boys, puberty is associated with an increasing plasma level of testosterone, which exerts direct virilizing and anabolic effects, leading to increases in bone mass and muscle bulk. In adolescent girls with aromatase deficiency, enhanced testosterone levels are associated with pseudohermaphroditism, virilization and polycystic ovaries (Morishima *et al.*, 1995; Meriggiola *et al.*, 2002).

Progesterone

Continuous administration of exogenous

progesterone to an adult female leads to interruption of ovarian cycles and blocking of ovulation. In the male, alterations of spermatogenesis can be induced by progesterone treatments (Jensen *et al.*, 2006).

Trenbolone acetate (TBA)

Hazardous effects of trenbolone acetate exposure were reported in the reproduction of both male and female mammals of various species. In the adult male, trenbolone acetate in direct administration induces a decrease in testis, seminal vesicle and prostate weights with alterations in spermatogenesis. In the adult female, such treatments induce virilization and alteration or suppression of ovarian cycles. In a study involving women volunteers given TBA showed disturbances of the menstruation cycle have been reported. Some data in rodents indicate that administration of trenbolone acetate during the intrauterine and perinatal period alters the reproductive function in adults (Jensen *et al.*, 2006).

Zeranol

Deleterious effects of zeranol exposure have been reported in reproduction of both male and female mammals of various species. In the adult female, such treatments induce alteration or suppression of ovarian cycles and endometrial hyperplasia. In the adult male, a sustained increase in the plasma level of zeranol administered by ingestion or implants induces a decrease in testis, seminal vesicle, prostate weights and alterations of spermatogenesis. (Newbold, 1999).

Melengestrol acetate (MGA)

Melengestrol acetate can block ovulation and the menstrual or estrous cycle in females from various species. In addition, it is capable of increasing the serum prolactin concentration of mice fed MGA at a daily rate of 0.2-0.8mg (Patterson *et al.*, 1989).

Anticipated effects of hormones in different stages

Certain studies have shown that even a small concentration of sex hormones (natural or synthetic) may be more injurious during developmental stages. During intrauterine and prenatal stages these hormones directly affect some organs like brain and primordial tissue architecture of the primary as well as secondary sex organs. During the embryogenesis fetal perinatal stages the administration of DES to laboratory animals has shown that this synthetic oestrogen is responsible in female mice for the following pathological entities: i) structural malformations of the oviduct, uterus, cervix and vagina; ii) salpingitis

thmicanodosa; iii) paraovarian cysts (of mesonephric origin); and iv) vaginal adenocarcinoma (Newbold, 1999). In addition to these anatomic and tissue-based malformations, infertility and sterility were observed in adult mice of both sexes. The administration of oestradiol to rodents during fetal and perinatal life resulted in significant defects in pituitary hypothalamic function in males. This in turn disrupted testicular function during adulthood involution of epididymal epithelium and seminiferous tubules with the absence of germ cells reduced testis size and reduced sperm production (Chang, 2012). It has been observed that this malfunction occurs during adulthood that leads to disrupt reproductive function.

There has been an increase in final height and a decrease in the age of puberty development in western countries during this century. Presently, this trend is generally attributed to the improved nutritional status in these societies. Interestingly, in a study including 17,000 girls between 3 and 12 years of age, signs of oestrogenic stimulation such as breast and pubic hair development have been observed in 27.2% of African-American girls and 6.7% white American girls at 7 years of age (Herman-Giddens *et al.*, 1997). This indicates that precocious puberty is somewhat common in the USA.

It has been suggested that cosmetic (hair) products, containing oestrogen or placenta extracts may be related to some of the increased prevalence of early puberty in African-American girls. However, the importance of environmental oestrogenic compounds present in plastics, insecticides and meat from animals treated with sex hormones, remains as only a possibility of affecting an early onset of puberty.

Conclusion

This paper provides a comprehensive review of different hormones used in cattle to increase the milk and meat production and their possibility to cause health issues in human being. There is lack of systematic study to support this issue, hence unable to directly relate the effect of these hormones on human beings. However, we conclude from the available literature that there is a certain impact on human beings such as cancer and premature puberty in girl children. Hence, more research is required in the areas like quantitative risks related to hormonal metabolites, carcinogenicity, genotoxicity of hormones as well as their metabolites. Further, a detailed study is required to determine whether the ingestion of IGF-1 is safe for children, adolescents during puberty and development of secondary sexual growth in adults.

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