Potential Risks and Benefits of Hormone Replacement Therapy.

Hormone replacement therapy (HRT) for menopause, andropause and premature gonadal failure, has been widely used to effectively relieve symptoms, such as hot flashes, vaginal atrophy, osteoporosis, decreased libido and sense of wellbeing by restoring hormone levels (Porth, 2005, p. 1060). The sex steroidal hormones commonly used include testosterone, estrogens, and progesterone in variable forms and compounds, individually or in combination and administered via different continuous or cyclic methods (Turgeon, Carr, Maki et al. 2006). Due to these variable factors it is unclear what the true benefits and risks of HRT may be, particularly as the patients in the trials and studies are of different ages and stages of life, have different genetic predispositions, medical histories and of course are individuals, with different nutritional and constitutional deficiencies and or strengths. In recent years, research has suggested that the benefits of HRT may be far outweighed by the level of risks associated with treatment for some people. The risks include but extend beyond the reproductive system to impact upon the cardiovascular, metabolic, neurological and musculoskeletal systems (Porth, 2005, p. 1060; Jones and Lopez, 2006, 185 – 188)

The risks of treatment with testosterone therapy range widely from the

relatively superficial, such as acne in both men (Porth, 2005, p. 1029) and women (Margo, 2006) and gynecomastia (Porth, 2005, p. 1029), to particularly damaging and in some cases life threatening risks, such as decreased high density lipoprotein (HDL) (Porth, 2005, p. 1029) and increased hepatoxicity due to the increase load on the liver (Margo, 2006). Jones and Lopez (2006) describe the possibility of testosterone therapy stimulating existing, unidentified prostatic malignancy or the increased risk of developing prostatic cancer (p. 188). Testosterone therapy also inhibits spermatogenesis (Davidson, 2006, p. 767) and in excess causes virilisation (Margo, 2006).

Increase in aggressive behaviour may be considered a risk of testosterone therapy, but Jones and Lopez (2006, p. 111) have suggested that it may not be testosterone that causes the aggression but that aggressive behaviour causes an increase in testosterone levels.

Increased erythropoiesis associated with testosterone treatment may increase risk of thrombosis, blood clots and infarctions, in persons with normal red blood cell indices, by increasing blood viscosity and altering normal haematological function. However, in those with low red blood cell count or at risk of anaemia, increased erythropoiesis may prove to be a healthful advantage (Snyder, Peachey & Berlin, 2000).

Further research has shown, in some cases, positive outcomes of testosterone treatment. In both men and women with deficient testosterone, libido and sexual interest (Davis, 1999) is increased with testosterone therapy (Jones and Lopez, 2006, p. 110; Snyder, et al 2000; Margo, 2006).
Men show proper erectile function and some have indicated an increase in the feeling of general wellbeing (Margo, 2006; Arlt, 2006) and energy levels (Snyder, et al. 2000). Bone mineral density is increased (Margo, 2006; Snyder, et al. 2000) through decreased urinary calcium excretion and decreased bone resorption. Positive effects have been shown on cardiovascular health markers particularly a reduction in total cholesterol (Isidori, Giannetta & Greco, 2005). Testosterone may play a positive role in metabolic syndrome. Treatment with testosterone has shown to increase insulin secretion and sensitivity, reduce abdominal obesity, increasing fat free mass and lean muscle tissue, improving body mass index (BMI) (Goulis, Tarlatzis, 2008). In a Japanese study a patient with Klinefelters syndrome treated with testosterone therapy increased insulin sensitivity by 50% (Ota, Suehiro, Ikeda, 2002).

The mixed results of many studies regarding the preventative or proliferative role of testosterone therapy in cardiovascular disease may be due to the variations in: the quantity and type of testosterone used, the extent of cardiovascular disease present at the onset of treatment, and the period of time elapsed since decreased endogenous testosterone and supplementation with exogenous testosterone (Isidori et al. 2005).

Davis (2005) suggests, aromatisation of testosterone to estrogen, may explain some of the success of testosterone treatment, particularly in women. Margo (2006) states, long term studies have not been completed in the areas of testosterone therapy risks, on heart disease and breast and prostate cancers.

The term Estrogen, includes 3 forms synthesised in the body. The most potent and physiologically active, estradiol, may reversibly convert to the less potent, estrone. The role of estrone increases as hormonal production in the ovaries is replaced by adrenal glands post menopause. The metabolism of both estradiol and estrone may irreversibly result in the weakest of the estrogens, estriol (Moskowitz, 2006, p. 210 - 212). Much research has been conducted under the banner of 'estrogen replacement therapy', however often the estrogen studied is synthetic, or completely foreign to humans, such as conjugated equine estrogens.

Unopposed estrogen therapy (ET; estrogen therapy without progesterone) has many risks that are usually dose dependant, and may or may not, decrease upon cessation of therapy. Unopposed estrogen therapy was the primary treatment for hormonally deficient women without a uterus (Moskowitz, 2006, p. 213).
Risk of developing endometrial cancer is increased six to fourteen times by treatment with ET for a minimum of one year and growth of benign uterine fibroids may be accelerated (Jones & Lopez, 2006, p. 186). Oral administration of ET has been shown to increase the secretion of angiotensin promoting vasoconstriction; it also increases the synthesis of liver proteins including coagulation factors, dramatically increasing the risk of stroke and blood clots (Moskowitz, 2006, p. 216). Development of atherosclerosis may be accelerated (Porth, 2005) and an increased risk of gallbladder disease (Jones and Lopez, 2006, p. 186) when using ET. In women 65 years of age or more, post hysterectomy, risk of dementia is also increased (Jones and Lopez, 2006, p. 185).
Estrogen dependant cancer such as breast cancer has been widely researched. The Million Woman Study of 2003 suggests ET alone holds less risk than combined therapy. The risks of breast cancer increase by 2.3% for each year a woman is receiving ET (Jones and Lopez, 2005, p. 185). Further research has shown the increased risk of developing breast cancer when taking ET for a minimum of 5 years as:

Ages 55-59 increased risk by 54
Ages 60-64 increased risk by 71 (Jones and Lopez, 2006, p. 185)

This Nurses study showed no change in breast cancer risk if ET continued for less than 5 years and that upon 5 years of cessation of therapy, risk of breast cancer is equal to those who have never had HRT (Jones and Lopez, 2006 p. 185). ET also increases occurrence of breast density (Moskowitz, 2006, p. 217). Risk of development of ovarian cancer is also significantly increased. Over a six year period of ET, risk of ovarian cancer increases to 40%, while over an eleven year treatment period, risk accelerates to 70% (Jones and

Lopez, 2006, p. 186).

The Women's Health program at Monash University (n.d.) explain ET increases sex hormone binding globulin (SHBG), when SHBG is increased, free circulating hormones may be bound decreasing their physiological activity, and this may reduce libido and sexual desire due to reduced free circulating testosterone.

As with testosterone therapy, estrogen therapy places an extra metabolic load on the liver.

Estrogen therapy is particularly beneficial in reducing common symptoms of menopause or ovarian failure of any origin, vasomotor fluctuations, insomnia, mucosal membrane dryness, vaginal atrophy. It stimulates secretion of cervical mucous, limits bone resorption (Porth, 2005, p. 1059) and may reduce incidence of fractures, however upon cessation of treatment the benefits to bone health diminish and bone loss is accelerated (Jones and Lopez, 2006, p. 185).
Bio Identical estrogen replacement therapy at low doses has shown to increase vasodilation and does not seem to increase systemic inflammatory markers (Moskowitz, 2006, p. 218).

Estrogen and progesterone combined therapy is recommended for women who have not undergone a hysterectomy. The progesterone opposes the proliferative effects of estrogen on the endometrial tissue (Moskowitz, 2006, p. 213). The benefits of reduced risk of malignancies of the endometrium may be outweighed by the increased risk of developing breast cancer (Jones and Lopez, 2006, 186 – 187). Combined therapy using the product PremPro® (synthetic conjugated equine estrogen CCE and medroxyprogesterone acetate MPA) was used in the Women's Health Initiative Study (Moskowitz, 2006 p. 209). This study was prematurely stopped when the risks passed the predetermined limits and the risks outweighed the benefits of treatment. Increased risks associated with this combined therapy include:
- 26% increase invasive breast cancer (Moskowitz, 2006, p. 209) greater risk than ET alone (Jones and Lopez, 2006, p. 185)
- 29% increased myocardial infarction or death from coronary heart disease (Moskowitz, 2006, p. 209; Jones and Lopez, 2006, p. 185)
- 41% increased risk of stroke (Moskowitz, 2006, p. 210; Jones and Lopez, 2006, p. 185)
- 200% increased risk for blood clots (Moskowitz, 2006, p. 210)
- increased risk of dementia in women over 65 (Jones and Lopez, 2006, p. 185)
- Increased risk gallbladder disease (Jones and Lopez, 2006, p. 186)

While the risks are alarming, benefits of combined therapy where found to include 33% decrease in hip fractures, inhibition of bone resorption and a 37% decrease risk of colorectal cancer (Moskowitz, 2006, p. 210). While we know that the benefits on bone health cease upon cessation of therapy, it is

unknown whether the protective role against colorectal cancer continues after therapy has ceased or not (Jones and Lopez, 2006, p.185). Combined therapy provides relief of symptoms of menopause such as hot flashes and vaginal atrophy.
It seems anthropometrics may play a role in the risks and benefits of hormonal replacement therapy as benefits may be increased in obese women while risks may be increased in thin women (Moskowitz, 2006).

Bloating, breast tenderness and irregular bleeding may be side effects of progestogen therapy. Progestogens are commonly prescribed without estrogen to balance 'estrogen dominance' a term describing either excess estrogen or deficient progesterone. Bio identical progesterone is widely used as a transdermal cream. Dioscorea villosa (wild yam) and soy contain saponins that are extracted and manufactured to produce bio identical progesterone. Suggested benefits of bio identical progesterone include effects on the cardiovascular system reducing hypertension by vasodilation and increased excretion of sodium through aldosterone antagonism, anti atherogenic action by reducing cholesterol ester formation and an anti proliferative effect on vascular smooth muscle and importantly, no increase in systemic inflammatory markers are associated with bioidentical progesterone treatment. Elevated cortisol levels have returned to normal limits with bio identical progesterone cream treatment. Effective reduction in breast tissue hyperproliferation due to estrogen exposure (Dzugan & Scipione, 2006, p. 53) and decreased frequency and severity of hot flashes are associated with bioidentical progesterone treatment (Moskowitz, 2006).

As with all synthetic introductions to the body the full ramifications often aren't completely understood. When progestin attach to progesterone receptors they bind adequately to provide some positive effects but may initiate unknown effects elsewhere in the body. An increase in the metabolic load of the liver is also a consideration in any hormone therapy. The 18 carbon tetra-cyclic hydrocarbon structure of some progestins are the parent structure of estrogens therefore it would be wise to consider estrogen risks factors also in progestin therapy (Moskowitz, 2006).

The obvious risks of undertaking conventional hormone replacement therapy have played a role in the search for completely natural alternatives to modulate a failing or imbalanced endocrine system. Phytoestrogens are a group of non-steroidal compounds found in plants, structurally similar to estrogens. They attach to estrogen receptors and may exert an estrogenic or anti estrogenic effect on the body (Murray, Pizzorno, & Pizzorno, 2005, p. 375-376) depending on patient hormone status and dosage (Mahady, 2005).
Phytoestrogens are found in the following foods:
- Soybeans and soy products (tofu, tempeh, soy milk, miso, soy proteins) -
- Flaxseeds
- Nuts
- Whole grains

- Apples
- Fennel
- Celery
- Parsley
- Alfalfa
- Herb red clover (Balch, 2006, p. 567)

Isoflavones, genistein and diadzein, are the most commonly used and extensively researched phytoestrogens (Isoflavones, 2008). In the presence of estrogen, phytoestrogens exert an anti estrogenic activity on endometrial tissue, antagonising the proliferative effect of estrogen by 10-20% (Mahady, 2005). This action may be explained by the weak estrogenic effect of phytoestrogens. In the presence of more physiologically active forms of endogenous estrogen, phytoestrogens attach to the receptor exerting a 'weak' hormonal effect while reducing available receptor sites for endogenous 'strong' estrogens (Murray et al. 2005, p. 374).

While phytoestrogens have been the focus of much research, clear guidelines for their safety are not defined, as the action cannot be confidently forecast. In women with, or those with a history of, estrogen receptor positive tumours, avoidance of soy isoflavone and soy protein is suggested as a conservative method of approach (Murray et al. 2005, p. 374).
The efficacy of soy isoflavones in balancing symptoms of estrogen deficiency has returned mixed results (Isoflavones, 2008), however the inclusion of soy wholefoods in traditional Asian diets is thought to play a role in the low rate of menopausal symptoms of local women (Balch, 2006, p. 567). Isoflavones have been shown to offer mild protection against osteoporosis, reduce vaginal dryness and reduce the severity of hot flashes (Isoflavones, 2008).

Persons of 'reproductive age' with premature gonadal failure will experience the same symptoms as woman in menopause or men with androgen deficiencies. It is thought that HRT in these cases may be used for longer periods of time before experiencing increased risk of morbidity (Jones and Lopez, 2006, p. 179).

Menopause may be asymptomatic for some woman and a traumatic experience for others. Common symptoms HRT is sought for include; hot flashes, night sweats, insomnia, vaginal atrophy, vaginal and skin dryness and osteoporosis. Taking into account what seems to be excessive increased risks of morbidity and mortality, with risk of developing breast, endometrial, prostatic cancer liver disease when using HRT, alternative treatments with less associated risk would obviously be ideal.

The complexities of the endocrine influences upon the human body are astounding and to assume 'a one fit for all' treatment protocol is particularly naïve in the case of hormone replacement therapy. The research that has been performed, as stringent as some may be, are limiting in potential for extrapolation as so many variables are at play. Before the potential risks and benefits of treatment protocols may be satisfactorily analysed these variables

must be accounted for. In particular the patients health status, age, family history and stage of life, differences in hormonal compounds, dosages and duration of treatment, method of administration and cyclic or continuous exposure. Hormone replacement therapy protocols require precise analysis of individual goals of treatment, and acute consideration of the potential benefits and risks. Unfortunately in the current time poor health system, this personalised process is not financially viable to many trying to navigate through the mixed information regarding hormone replacement therapy. General public recommendations bravely suggest, in what appears to be a "fingers crossed' approach, the lowest dose of hormone therapy for the shortest period of time to achieve treatment goals.

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