

## Bioidentical Hormone Preparations - History of Development

The use of the terminology 'BIOIDENTICAL HORMONE' therapy has aroused much controversy and heated debate over the past 20 years, often with much criticism and unreferenced claims from the various protagonists.

Major concerns are directed towards a growing trend by compounding pharmacists to promote the use of bioidentical oestrogen and bioidentical progesterone as being 'natural' and therefore superior to 'synthetic' hormone therapy. To add to the concerns is the promotion of these 'natural' hormones using delivery systems such as troches and creams. While there is evidence that both routes of delivery are viable, there is very little evidence that HRT delivered in this formulation is able to achieve physiological levels capable of inhibiting osteoporosis, a reduction in cardiovascular damage or a positive influence on neurological function.

It is for that reason the Australasian Menopause Society is reviewing the major points of dissension in the debate and providing information and data regarding bioidentical hormones to allow women and their health care providers with the knowledge that will allow them to make an informed decision as to reasons to use any of the various forms of HRT including compounded bioidentical therapy.

### Oestrogens

**Physiology** The ovary of a young menstruating woman secretes large amounts of oestradiol from the granulosa cells surrounding an egg in the ovary, in a regular pattern during each menstrual cycle (The amount of natural oestradiol produced by the ovary can vary from 70 mcg /day to 500mcg /day depending on what stage of the cycle is sampled. Oestradiol is measured in circulating blood and the amount detected is expressed in picomols/litre). However, the very potent primary oestradiol is rapidly metabolised by enzymes in target cells and the liver to the weaker oestrone hormone before finally being degraded to oestriol. The majority of all oestrogens circulates as the inert oestrone sulphate but this can be easily metabolised to oestrone by enzymes in target organs.

The stepwise degradation of oestradiol occurs independently of the source or amount of the hormone – whether it is administered from an exogenous or an endogenous source. For that reason the ratio of the levels of oestrone and oestriol to the parent oestradiol remains relatively constant depending on the presence and amount of dehydrogenase enzyme in cells. So the amount of oestradiol, oestrone, oestriol or oestrone sulphate is controlled by the presence and availability of enzymes – not some doctor or pharmacist who arbitrarily decides that he/she knows what levels should be in circulation. The levels of oestrogens detected in circulation are continually being modified by the activity of enzymes no matter from whatever source or dosage the oestrogen originates.

For that reason, it is futile for doctors to write prescriptions for, or pharmacists to dispense, all three hormones (bi-gest, tri-gest) in an attempt to emulate what nature does naturally.

## Historical development

### Oestrogen

Oestradiol, oestrone and oestriol were all identified by the mid 20's and attempts were soon made to manufacture these products for clinical use. In the early 1930's, the cost of even minute amounts of natural oestradiol was so expensive that, when it was also realised that oral oestradiol was rapidly degraded in the gut and the liver, it was apparent that natural oestradiol was not a viable hormone for clinical use. For that reason a number of attempts were made to synthesise a steroid compound with oestrogenic activity.

In 1936 Prof. Dodd in Oxford invented stilboestrol while in Germany in 1938, Drs. Inhoffen and Hohlweg realised that by adding an ethinyl molecule to oestradiol a stable oestrogenic compound (ethinyl estradiol) could be developed. These stable synthesised compounds were able to reproduce all the action of natural oestrogen but were slowly degraded and excreted and therefore a much lower dose of the hormone could be used to obtain the same response as a natural oestrogen. Although ethinyl oestradiol is ideal as a low dose oestrogen for oral contraception, its potential to develop adverse events made it less than ideal for post-menopausal women.

In 1938 the pharmaceutical company Wyeth began extracting equine oestrogen from pregnant mares' urine. The majority of oestrogen in pregnant mares' urine is oestrone sulphate – identical with the oestrone sulphate in humans and this product quickly became the most commonly used oestrogen in the USA. It is the commonest oestrogen used in menopause research studies in America and is often regarded as being a 'natural' oestrogen.

In a further attempt to inhibit the degradation of bioidentical oestradiol by the dehydrogenase enzyme, various esters of oestradiol were synthesised and developed. A typical ester molecule still in popular use is oestradiol valerate (Progynova) developed in the early 1950's. Once ingested, the oestradiol ester is metabolised in the liver to valeric acid, plus bioidentical oestradiol. The bioidentical oestradiol from Progynova acts, and is metabolised in the same way as natural oestradiol and for over 50 years, has been shown to be a most effective and safe method of delivering bioidentical oestradiol to a post menopausal woman. Other esters and modified oestrogens have been synthesised and are being used extensively following considerable research and clinical trials.

To continue obtaining the benefit of bioidentical oestradiol and avoid the problem of degradation of the oestrogen molecule in the gut, commercial pharmaceutical companies have designed transdermal patches, creams and gels containing measured amounts of bioidentical oestradiol and conducted considerable clinical long-term studies to demonstrate that this method of administering oestrogen is safe and effective.

## Progesterone

Progesterone is produced by the corpus luteum of the ovary following ovulation, and from the placenta in pregnancy. Its main purpose is to induce a secretory change to the endometrium, to prepare the endometrium for implantation and maintenance of a pregnancy and to develop and mature breast glands.

The amount of progesterone measured in the circulation is reported in nanomols/litre (1 nanomol is equivalent to 1000 picomols). The amount of natural progesterone produced from the ovary and found to have a positive effect on the endometrium has been measured in the circulation in the luteal phase of a menstrual phase and varies from 15-100 nanomols/litre daily (15,000 -100,000 picomols).

Progesterone is very rapidly degraded in the human gut, liver and circulation so it has been difficult using oral therapy to maintain a level of progesterone sufficient to protect or change the endometrial cells, to inhibit hyperplasia or prevent cancer in the endometrium.

Progesterone can be absorbed through the skin in amounts similar to that achieved with oestrogen, but the amount circulating (1-3 nanomols/litre) after a measured amount of progesterone cream has been applied to the skin, is insufficient to have any effect on the endometrial cells.

There is some evidence that progesterone can be absorbed through the vaginal epithelium and through the buccal mucous membrane, but at present there are no reliable studies available to confirm that the amount absorbed from this source has a protective effect on the endometrium.

## Synthetic progestogens

Because of the unreliable absorption of progesterone by any route, efforts were made in the 1950's to develop a synthetic product that would have a progesterone-like effect on the endometrium. The most commonly used of the many progestogenic products developed was medroxy progesterone acetate (Provera in the USA), nor-ethisterone (Primolut-N in Europe) and levonorgestrel. Over the past 20 years a number of other progestogens have been invented in an attempt to reduce the side effects attributed to their use.

These synthetic progestogenic compounds all inhibit growth of the endometrium in varying doses and all suppress the hypothalamic/pituitary/ovarian cascade, so were ideal to form the basis of oral contraceptive therapy as well as for other gynaecological treatments. The problem with progestogens has been the development of adverse side effects, among which are depression, loss of libido, weight gain, fluid retention, bloating, breakthrough bleeding and possibly an increase in breast cancer.

It is because of these adverse events caused by synthetic progestogens that interest has once again been directed to the bioidentical hormones but particularly to bioidentical progesterone.

Progesterone is only found naturally in females who have functioning ovaries. However, bioidentical progesterone can be manufactured in a laboratory by a unique chemical process involving

converting a precursor, called diosgenin, using a sequence of enzymatic actions. This synthesis of bioidentical progesterone was invented in 1938 by a brilliant chemist (Russell Marker) and its manufacture allowed clinicians to have access to a relatively cheap and available source of this hormone. However, the commercial availability of bioidentical progesterone was limited by the availability of diosgenin. Marker began exploring for plants that contained diosgenin and among those having this chemical, found the highest amount to be present in the Mexican wild yam.

One of the unfortunate side effects of this discovery is that some charlatans and 'snake oil' salesmen have 'conned' some women into believing that a cream based on Mexican wild yam contains some ingredient that will have a beneficial effect on menopausal symptoms. These claims are untrue. Diosgenin, as well as Mexican wild yam cream, has no beneficial effect on the menopause unless a complex enzymatic synthesis converts it into an hormone.

Although bioidentical progesterone added to oestradiol is considered as the most ideal agent for hormone therapy, with no apparent adverse side effects, it is very difficult to maintain a circulating blood level sufficient to inhibit endometrial proliferation.

## Route of delivery

When it was realised that oral administration of a synthesised oestrogen or a synthetic progestogen often resulted in adverse effects, alternative means of delivery were explored and the skin was targeted as a likely route of delivery.

Because only relatively small amounts (150-1000 picograms) of oestradiol are required to control symptoms, maintain a moist vagina, inhibit osteoclastic activity and maintain arterial endothelium, the amount of oestradiol absorbed through the skin, the vaginal epithelium or the mucous epithelium from patches, gels, creams or lozenges, is capable of inhibiting symptoms and maintaining cell activity.

Adequate levels of circulating oestradiol are achieved (150-1000 picomols/litre), by the transdermal route, and because the gut and liver are avoided, there is less metabolic degradation of oestradiol, there is a positive general response and less risk of adverse effects. The other advantage of a transdermal application is that a patch, cream or gel of oestradiol applied to the skin allows a constant but low absorption as opposed to the high, short-term, bolus effect from an oral administration of the same oestrogen.

Unfortunately the same beneficial effect using transdermal therapy cannot be said for progesterone. To obtain sufficient bioidentical progesterone (5,000-30,000 picomols/litre) through the skin would necessitate applying huge amounts of cream or a gel to the skin, while it would be impossible to manufacture a patch large enough to allow sufficient bioidentical progesterone to be absorbed to protect the uterus.

Another portal of entry that has been explored for both bioidentical oestradiol and bioidentical progesterone includes the mucous membrane of the mouth. This method requires the hormone to be compounded as a lozenge (or troche) that is sucked over a period of 20-30 minutes without swallowing the saliva.

Both bioidentical oestradiol and bioidentical progesterone are readily absorbed into circulation using the buccal mucous membrane route, but the clinical effects are variable. In a study using both bioidentical oestradiol and progesterone in a troche and conducted over 12 weeks (Wren, Gross et al) it was demonstrated that flushes, sweats, moods and vaginal epithelium all improved but there was no apparent response in bone indices, cholesterol measures or endometrial cells. The level of oestrogen was markedly elevated for about 1-2 hours but quickly subsided to the base level, while the circulating progesterone level was mildly elevated for 2-4 hours after using a troche but returned to base-line after 5 hours. Whether this amount of progesterone is sufficient to have a protective secretory effect on the endometrium has never been determined.

The problem with transbuccal therapy (troche) is that no dose dependent studies have ever been conducted. No one can advise just what the minimal or maximum dosage of oestrogen or progesterone is required in a troche in order to maintain cell activity without inducing an abnormal response or an adverse effect. The amount of progesterone in circulating blood required to convert the endometrium into a secretory pattern is unknown and the risk of break-through bleeding has not been noted, but there are at least three known cases of uterine cancer arising in women who used bioidentical progesterone as a cream or troche.

What has been noted is that many prescriptions for a troche have been written by general practitioners following advice from a compounding pharmacist. Neither the doctor nor the pharmacist has any reputable scientific or clinical evidence that such a regimen of treatment has the desired long-term benefit or has no adverse effect. This is clearly unethical and fraught with potential litigation if any adverse event occurs.

It is important to realise that all bioidentical hormones are synthesised. No hormone used in any preparation (regular HRT or compounded therapy) is 'natural' – they are all synthesised from some precursor by the action of enzymes. Both regular and compounded hormone therapies use bioidentical oestradiol but because of its rapid degradation and unsafe endometrial response, bioidentical progesterone is not used by commercial pharmaceutical companies.

Because of the lack of scientific evidence, because of the misuse of data from hormone regimens designed by commercial pharmaceutical companies and because of misleading statements regarding the difference between 'synthetic' hormones and bioidentical hormones the Australasian Menopause Society does not endorse the use of compounded bioidentical hormone therapies.

See Information Sheet Bioidentical Hormones for Menopausal Symptoms

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