INTRODUCTION: Personalised Medicine – Compounding as a Means to this End

With major investments in scientific research and the growing advances in healthcare and diagnostic testing, personalised medicine is on the exponential rise. Now more than ever before, patients are seeking unique therapeutic options that are tailored to their specific needs and requirements. The need for this customised approach is gaining scientific support as empirical reports on genetic and biological markers for specific conditions and disease states continue to accumulate. While there still remains much to be learned on the significance of certain genetic and biological markers, the trend of current findings reveal that individual variations play a profound role in the development, progression, and consequently the treatment of pathology. **Personalised medicine** refers to medical decisions, practices, and interventions that are tailored to an individual patient based in individual pathological markers, symptoms, treatment response, among many other factors. Given that pharmacotherapy contributes significantly to a treatment intervention, customized pharmaceuticals is in growing demand.

According to the Guideline on Compounding of Medicines by the Pharmacy Board of Australia, **pharmaceutical compounding** refers to:

> "The extemporaneous preparation and supply of a single 'unit of issue' of a therapeutic product intended for supply for a specific patient in response to an identified need."

Pharmaceutical compounding allows pharmacists and licensed practitioners the flexibility to create a medication that is designed to fit the unique and specific requirements of a practitioner's therapeutic plan for an individual patient. Compounding is the art and science behind customised pharmaceuticals and by these lines, serves as a means to an end for personalised medicine. Among its many possibilities, pharmaceutical compounding allows the one flexibility to:

- Address the challenges and limitations of manufactured products (e.g., discontinued medicine, one-size-fits-all).
- Adjust the dosage strength of a medication.
- Reformulate and modify the dosage form (e.g., developing a transdermal dosage form to replace a solid oral dosage).
- Combine multiple ingredients, thereby simplifying a dosing regimen.
- Exclude certain ingredients to eliminate unwanted side effects and intolerances.

➢ ***Refer to Appendix D for Australian Policy Guide on Compounded Medications***

SECTION I: Fundamental Principles and Rules of Engagement

The following principles will become very helpful in gaining a firm understanding of, not only the subject of hormone restoration and balance, but more so, how it is treated. Subsequent to gaining an understanding of these series of fundamental principles, we will understand how rules are established.

The fundamental principles include:

1. Restoration and Balance
2. Relative versus Absolute
3. Balance and Relative Sensitivity
4. Free versus Bound
5. Up and Down Regulation
6. Agonist, Antagonist and Synergistic Activity
7. Pharmacokinetic versus Pharmacodynamic Balance
8. Cyclic versus Continuous Dosing
9. Routes of Delivery and Delivery Systems
10. Monitoring Frequency and Therapeutic Intent
11. Minimum Dose for Maximum Effect

1. Restoration and Balance

- Restoration and balance are essential functions as it applies to hormonal homeostasis.
- Hormone levels and receptor sites, combined, are in constant flux.
- Cyclical patterns seen in hormonal homeostatic mechanisms create a moving target.

Rule for Restoration and Balance:

Ascribe hormone treatments that restore deficiencies and bring balance to the homeostatic mechanism within the female or male reproductive life cycle.

Supplemental Reading:

The human body maintains homeostasis via an array of mechanisms and restoration and balance are two of its essential functions. The endocrine system is a dynamic arrangement with hormone levels changing regularly depending on the time of day, the time of month, changes in the intrinsic and extrinsic environments, among other factors. Moreover, these changes in hormone levels are directly correlated to changes in the number of available receptor sites (Handa, 1994). Receptor sites are sometimes specific to a given hormone and other times they are shared between hormones. In the latter circumstance, one hormone typically has greater or lesser affinity for the receptor site than the other (Klinge, 2001). Furthermore, as the number of hormone molecules received at their respective receptor sites changes, so too does their production capability (Handa, 1994). The hormones and receptor sites combined are in constant flux, undergoing perpetual change. Sometimes the body is unable to restore hormones to their desired levels and consequently it cannot restore a sense of balance. Attempts to maintain homeostatic balance that is offset typically involves the application of a significant exogenous factor…hormone therapy!

The fluctuating cyclical patterns seen in hormonal homeostatic mechanisms, in effect, create moving targets for the clinician (Czeisler, 1998; Fuleihan, 1997). The goal of the clinician and compounding pharmacist are to make appropriate adjustments in treatment as it relates to this moving target until a new balance between the effect of the endogenous and exogenous systems and symptoms lead to the desired physiological effect and clinical outcome. It is this moving target that carries a great deal of weight when a clinician attempts to restore and bring a new sense of balance to the endocrine system on a patient-specific basis.

Unlike many other treatments, hormone restoration and balance is, for the most part, a long-term journey the clinician must take along with their patients. This mere fact lends itself to the study of the long-term effects of your pharmacotherapeutic interventions. Not only are we responsible for the restoration and balance of hormonal levels and system functions, but we must also demonstrate responsibility for the balance that exists between treatment for the prevention of other conditions, such as Alzheimer's Disease (Shao, 2012) and osteoporosis (Torgerson, 2001; Mosekilde, 2000), as well as the cancer-related risk factors associated with long-term hormone therapy.

2. Relative versus Absolute

- There is a range of normality for hormones.
- Absolute and relative values of two hormones undergo a balancing act every minute.
- The effect of absolute and relative hormone values on overall homeostatic mechanisms needs to be evaluated.

Rule for Relative versus Absolute:

Concurrently assess absolute hormonal levels, as well as their relative qualifiable and quantifiable relationships to one another.

Supplemental Reading:

Given individual genetic predispositions, there tends to be a range of normality for any given hormone (Gray, 1991). Given exogenous and / or endogenous factors, the absolute value of any hormone can fall within, rise above, or fall below its normal range.

Depending on the effects of altered hormonal levels, it may be decided that treatment is required. When reviewing the level of any hormone, the clinician must evaluate the absolute and relative effect of hormones on the homeostatic mechanisms. It is often the interaction and interplay between hormones that determine the physiological effect on the homeostatic mechanism. Both the absolute values and the ratios between specific hormones must undergo review and is a fundamental component of the basis for which therapeutic intervention is determined (Supornsilchai, 2003).

The changes in absolute and relative values of two functional entities undergo a balancing act every minute of every day; a virtual seesaw or teeter-totter. This is what constitutes the homeostatic mechanism. When the homeostatic mechanism fails, it is often deemed necessary to treat this imbalance with exogenous hormones (Rohr, 2002). It must be further recognized that the addition of these exogenous hormones will have a further effect on the homeostatic mechanism, which may also affect the relative and absolute values of yet other hormones within the larger homeostatic mechanism. Despite the fact that we now have numerous moving targets in constant flux, most of them are measurable, nonetheless. These moving targets are the relative and absolute values of hormones in the body.

3. Balance and Relative Sensitivity

- Recognize the effect of hormone metabolites and the potential for deleterious side effects.
- Recognize a patient's relative sensitivity to a given treatment protocol.
- Recognize the need for frequent monitoring.

Rule for Balance and Relative Sensitivity:

Be aware of the innate differences between individuals as it applies to the sensitivity of the relative relationship between any two hormones.

Supplemental Reading:

As it applies to hormone treatment, until the newly desired homeostasis is reached, frequent monitoring becomes necessary. This is particularly pertinent for hormones whose absolute therapeutic range are narrower. Given the complexity of genetic factors on the overall homeostatic mechanism, attaining and maintaining balance has a varied patient-specific sensitivity. The interaction of genetic factors, lifestyle, diet, among an array of other personal factors, on the homeostatic mechanism is referred to as the patient's relative sensitivity to a given treatment protocol (Andersen et al., 2002).

Adding exogenous hormones to the homeostatic mechanism without recognizing the effect of their metabolites can cause deleterious side effects and render your hormone therapy initiative harmful.

Furthermore, feedback loops within the homeostatic mechanism often leads to decreased sensitivity or ability of the exogenous hormones to achieve their desired physiological effect.

4. Free versus Bound

- Free drugs are biologically active.
- Bound drugs make up the reservoir.
- Sex Hormone Binding Globulin plays a key role in hormone availability.

Rule for Free versus Bound:

Qualify and quantify bound and bioavailable hormone levels on an ongoing and consistent basis.

Supplemental Reading:

Free drug is considered to be available to interact with receptors and is thus considered biologically active. **Bound drug** can be divided into two relative categories – bioactive and reservoir. Loosely bound drugs in the plasma can be considered to be biologically active if the bond between the protein molecule and hormone is easily broken. Relative binding affinities can affect the rate of release and thus the degree of biological activity (Tripathi, 2013). Bound drugs are considered reservoir when either the site of binding or the affinity to bind affect the release of the hormone. Hormones that are metabolized to a storage form that require a reverse of this metabolic function prior to their release are difficult to release (Tripathi, 2013).

Hormones are typically stored in tissue; the greater the amount of tissue the larger the hormone depot and the lesser the amount of tissue the smaller the hormone depot. The size of the depot is a significant factor in both immediate treatment protocol establishment and long-term effects (Tripathi, 2013).

Certain hormones have higher affinities to various binding proteins and some binding proteins can be influenced by the amount of hormone present in the body. For example, oestrogen and testosterone bind equally at approximately 70% to the binding protein, Sex Hormone Binding Globulin, and DHEA binds to albumin at approximately 80%. Additionally, high body oestrogen levels can increase the Sex Hormone Binding Globulin formation thus increasing the binding of testosterone (Tripathi, 2013).

5. Up and Down Regulation

- Receptor sites play a critical role in maintaining homeostatic balance.
- Receptors are regulated by endogenous homeostatic mechanisms.
- Exogenous hormones and their metabolites cause down regulation of receptor sites.

Rule for Free versus Bound:

Qualify and quantify bound and bioavailable hormone levels on an ongoing and consistent basis.

Supplemental Reading:

Receptor sites play a critical role in maintaining homeostatic balance. They can be slightly different in their design or have a different range of affinities to hormones due to genetic predisposition. Receptors are regulated by endogenous homeostatic mechanisms to make them more or less available to interact with bioavailable hormones and their metabolites (Briggs & Christie, 2014).

Typically, over time, exogenous hormones and their metabolites cause down regulation of receptor sites or existing active receptor sites are rendered less or non-responsive to the exogenous hormone; referred to as desensitizing or tolerance effects. Once this down regulation takes place, increased dosing will not have the desired effect since the receptors initiating or maintaining receptors is no longer available or capable of this activity (Briggs & Christie, 2014).

Up regulation of receptors or sensitization of receptors can be caused by exogenous hormones if these receptors are dependent upon the availability of the specific exogenous hormone or their metabolites (Briggs & Christie, 2014).

6. Additive, Synergistic, and Antagonistic Activity:

- Most hormones work with other hormones to produce additive, antagonistic, or synergistic effects (*refer figure 1)*.
- **Additive activity**: When two or more substances produce a total effect that *equates* to the sum of each substance's individual effect (Moscou and Snipe, 2014).
- **Synergistic activity**: When two or more substances produce a total effect that is *larger* than the sum of each substance's individual effect (Moscou and Snipe, 2014).
- **Antagonistic activity**: When two of more substances produce a total effect that is *less* than the sum of each substance's individual effect (Moscou and Snipe, 2014).

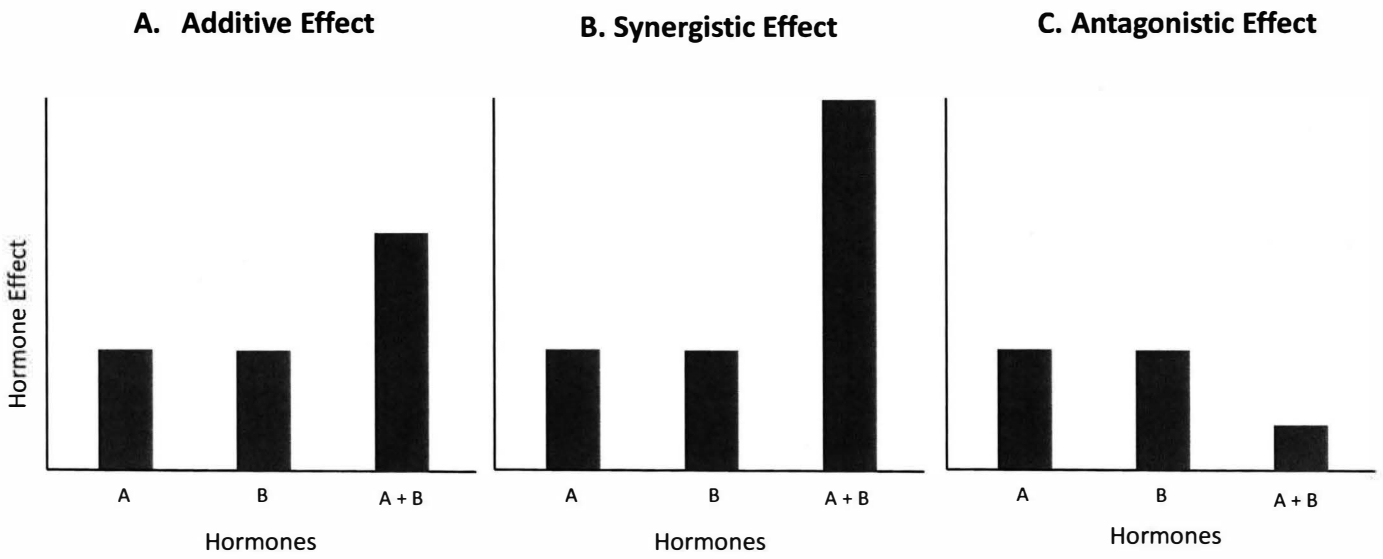


Figure 1. Graphical depiction of additive, synergistic, and antagonistic interactions

Rule for Additive, Synergistic, and Antagonistic Activity:

Consider the impact of additive, synergistic, and antagonistic interaction of hormones and their concomitant impact on cellular and tissue proliferation.

7. Pharmacokinetic versus Pharmacodynamic Balance

- Always consider pharmacokinetic and pharmacodynamic factors.
- There exists a complex interplay between absorption, distribution, metabolism, and excretion.

Rule for Pharmacokinetic versus Pharmacodynamic Balance:

Provide adequate and equitable consideration for the impact of what a drug agent is doing to the body and what the body is doing to that same drug agent.

Supplemental Reading:

Consideration must always be given to the principles of pharmacokinetics and pharmacodynamics; what the body does to a drug versus what a drug does to the body. Much of this dynamic interaction can be explored by looking carefully at the absorption, distribution, metabolism, and excretion of a drug.

Absorption directly affects a substance's bioavailability. It is determined by the physical and chemical properties of an active agent and the excipients in a delivery system. Of particular interest is the drug agent's acidity or basicity, ionization, and water or lipid solubility. Unless administered IV, a drug agent must cross several semi-permeable membranes before it reaches the systemic circulation. It is the membrane's bimolecular lipid matrix which determines membrane permeability that selectively inhibits passage (Meibohm, 2013).

Distribution of drug agents is influenced by their binding capacities to proteins and lipids, blood perfusion into tissue, and cell membrane permeability. The entry rate of a drug into a tissue is dependent upon the rate of blood flow through tissue, tissue density, and partition characteristics between blood and tissue. For poorly perfused tissues distribution is very slow, especially if the tissue has a high affinity for the drug (Meibohm, 2013).

Distribution of drug agents from tissues into the blood stream is directly related to serum protein and tissue binding and is transported partly in solution as free or unbound drug and partly reversibly bound to blood components such as serum proteins and blood cells. Only unbound drug is further available for passive diffusion into tissue sites. 'Lipid loving' drugs often bind to fat resulting in a longer equilibration time, especially if the drug is highly lipophilic. Drug storage in fat initially shortens the drug's effect. However, over time, it will eventually prolong the effects (Meibohm, 2013).

Metabolism takes place primarily in the liver; however other organs such as the intestines, skin, and lung can also metabolise drug agents. Although metabolism most often inactivates drugs, some drug metabolites are pharmacologically active (Meibohm, 2013).

Excretion of most active drugs and their metabolites is as a result of kidney filtration. However, drugs bound to serum proteins will remain in the circulatory system (Meibohm, 2013).

As the pharmacokinetic and pharmacodynamic characteristics of drug agents and the body are explored a complex interplay is realized; that one of these subjects cannot be evaluated without consideration for the other.

8. Cyclic versus Continuous Dosing

- The decision to prescribe hormones in a cyclic versus continuous dosing manner is currently divided.
- There may exist a time and / or place for both cyclic and continuous dosing approaches.

Rule for Cyclic versus Continuous Dosing:

Determine the absolute and relative short- and long- term significance of cyclic versus continuous hormone administration.

Supplemental Reading:

This particular topic is philosophical in nature and often controversial. We are going to keep it that way throughout the program. Until such time as long-term studies prove superiority, one approach over the other, there will continue to be a divergence in philosophical guidelines for the treatment of hormone restoration and balance.

The decision to prescribe hormones in a cyclic versus continuous dosing manner is divided and, for the time being, may end up being a personal preference. Long ago when a progestin was added to oestrogen therapy, it was always cyclic. The routine was to give oestrogen during days 1 - 25 of the calendar and add progestin on days 14 - 25. That would leave day 26 to the end of the month as a hormone free interval. Most women would still have a withdrawal bleed during that time, and some women were very symptomatic with four or more days off oestrogen. As a result, the oestrogen was prescribed on a continuous basis, but the progestin was still given the same way. After some research studies confirmed that there was no increased risk of endometrial hyperplasia with continuous dosing, the dosage of progestin was decreased and was also given continuously. The lower dose of progestin helped to decrease its side effects, and the continuous dosing eliminated the withdrawal bleed in most women. When the shift toward using more bio-mimetic hormones took place, the practice of continuous dosing was maintained. It is usually recommended to have four hormone free days per month, either all at once, or one day a week, to prevent tolerance at the receptor site. For the patient who continues to have a withdrawal bleed after menopause, it becomes difficult to discern between physiologic and pathologic bleeding (Vlahos et al., 2013).

9. Routes of Delivery and Delivery Systems

- The partition coefficient of a hormone from a base is a critical variable in base selection.
- Lipid-soluble hormones more easily penetrate cell membranes and subsequently bind to their target receptors.
- Solubility factor determines the mechanism by which a hormone molecule acts on its target cell or tissue.

Rule for Routes of Delivery and Delivery Systems:

Determine the rate of absorption and subsequent bioavailability from known and / or hypothesized partition and diffusion coefficient-related variables.

Supplemental Reading:

In hormone therapy, as is the case with any atypical segment of pharmacotherapy, there exist a number of routes of delivery from which drug agents may be administered. The most common routes of delivery for hormone therapy include **oral**, **rectal**, **vaginal,** **topical**, and **sublingual**. Each route of delivery has its advantages and disadvantages from too slow or too fast acting, to first pass effect being by-passed or not, to local versus systemic effects, and to the manner in which the drug agent will interact with the body and how the body will react to the presence of the drug agent (Goodman, 2012; Grant & Leone-Bay, 2012; Fantasia & Sutherland, 2014).

With each route of delivery there are numerous delivery systems and respective compositions that will result in intersystem variability as far as rate of absorption is concerned. While the **diffusion coefficient** is of concern when we speak of the route of delivery, it is the **partition coefficient** that need be addressed when a delivery system is selected. Partition coefficient refers to the rate of release of a drug from the delivery system's base and the subsequent rate of absorption of the drug agent through the tissues. Together these rates of diffusion determine serum levels of the drug agent at any instant in time. It is the capture of that same serum level at multiple time intervals that will reveal a critical aspect of the drug agent's bioavailability and corresponding potential for therapeutic effect; its onset and duration (Meibohm, 2013).

Hormones can be classified into a number of categories (Grant & Leone-Bay, 2012):

- **Amine hormones** are small molecules originating from amino acids (e.g., thyroid hormone).
- **Steroid hormones** in all instances are derivatives of the precursor steroid cholesterol (e.g., testosterone and oestrogen).
- **Peptide and protein hormones** are the largest and most complex of hormones (e.g., insulin).

Hormones are either lipid-soluble or lipid-insoluble. It is this solubility factor that determines the mechanism by which a hormone molecule acts on its target cell or tissue. Seeing as how drug agents need be in solution to by-pass many tissue barriers, in particular the stratum corneum in the case of transdermal applications, the selection of base components is an important consideration in the design of an appropriate delivery system.

Lipid-soluble hormones more easily penetrate cell membranes and subsequently bind to their target receptors. Lipid-soluble hormones often act on DNA, inhibiting and stimulating the transcription of specific proteins. This hormone-DNA interaction can have effects on the body's overall function for hours and in some cases days. A lipid-insoluble hormone and its inability to penetrate the cell membrane require secondary messengers which translate the outer message and functions though the cell membrane to its secondary target.

10. Monitoring Frequency and Therapeutic Intent

- There exists an initial hormone level of bound and free molecules that represent reservoir and bioactive modes, respectively.
- Many factors contribute to the absolute and relative levels of hormones within the homeostatic mechanism.

Rule for Monitoring Frequency and Treatment Regimens:

Monitor and subsequently adjust treatment protocols to minimize the quantity of hormones delivered, while attempting to maximize therapeutic effect and reduce or avoid completely the potential for long-term side effects.

Supplemental Reading:

The endocrine system is perhaps one of the more complex systems of human physiology. One single perspective of this system is clear; subsequent to administration of hormones there exist levels of bound and free molecules that are in reservoir and bio-active modes. Each need be monitored for their potential therapeutic and side effect profiles. Rate of tissue perfusion, absorption, distribution, metabolism, excretion, reservoir capacity and the impact of absolute and relative levels of hormones, receptor site affinity, etc… all contribute to a system in perpetual flux. This truly makes hormone therapy a moving target (Meibohm, 2013).

11. Minimum Dose for Maximum Effect

Rule for Minimum Dose for Maximum Effect:

Where applicable, always apply the most minimal dose that produces a maximal therapeutic effect.

Summary of the Fundamental Principles and Rules of Engagement for Hormone Restoration Therapy

Fundamental Principle	**Rule of Engagement**
1. Restoration and Balance	Ascribe hormone treatments that restore deficiencies and bring balance to the homeostatic mechanism within the female or male reproductive life cycle.
2. Relative versus Absolute	Concurrently assess absolute hormonal levels, as well as their relative qualifiable and quantifiable relationships to one another.
3. Balance and Relative Sensitivity	Be aware of the innate differences between individuals as it applies to the sensitivity of the relative relationship between any two hormones.
4. Free versus Bound	Qualify and quantify bound and bioavailable hormone levels on an ongoing and consistent basis.
5. Up and Down Regulation	Assess prescribed hormone levels in order to rationalize the potential impact on up and down receptor site regulatory mechanisms.
6. Additive, Synergistic, and Antagonistic Activity	Consider the impact of additive, synergistic, and antagonistic interaction of hormones and their concomitant impact on cellular and tissue proliferation.
7. Pharmacokinetic and Pharmacodynamic Balance	Provide adequate and equitable consideration for the impact of what a drug agent is doing to the body, and what the body is doing to that same drug agent.
8. Cyclic versus Continuous Dosing	Determine the absolute and relative short- and long-term significance of cyclic versus continuous hormone administration.
9. Routes of Delivery and Delivery Systems	Determine the rate of absorption and subsequent bioavailability from known and/or hypothesized partition and diffusion coefficient-related variables.
10. Monitoring Frequency and Therapeutic Intent	Monitor and subsequently adjust treatment protocols to minimize the quantity of hormones delivered, while attempting to maximize therapeutic effect and reduce or avoid completely the potential for long-term side effects.
11. Minimum Dose for Maximum Effect	Where applicable always apply the most minimal dose that produces most maximal therapeutic effect.

Your Philosophical Guideline

We advocate the implementation of safe treatment protocols for short- and long- term goals and objectives encompassing a holistic approach that includes lifestyle management and preventative interventions when and where they are appropriate and justified.

TO RESTORE

By incrementally adding the minimum amounts of any hormone required in an attempt to reduce or eliminate symptomatology, replenish deficiencies, or prevent the onset of age-related diseases.

TO BALANCE

By restoring the correct amount of one hormone always taking into account its impact and further need for other hormones, always considering the overall homeostatic mechanism.

TO PATTERN

By determining the need for cyclic versus continuous dosing, avoiding off-setting naturally occurring rhythms, replacing deficiencies, and bringing balance to the overall homeostatic mechanism.

TO ADJUST

By regularly monitoring subjective symptoms and performing objective tests on hormone levels to minimize dosing, while striving to achieve the best possible therapeutic outcome. Be cognizant of your ever moving target and when treatment should end.

TO MINIMIZE

By applying the minimum amount of hormones necessary to achieve the maximum therapeutic outcome, never neglecting the potential for long-term side effects

Note: In the case of any and all treatment administration as outlined in this seminar, the protocols assume no particular delivery system or base. The appropriate delivery system may require further modification to the suggested treatment protocol. Therapy must be made on the basis of a combination of prior medical history, familial history, clinical assessment, symptom assessment, and hormone level range testing results. Continuous assessment and testing is required to maintain dosing regimen within acceptable margins. A healthcare provider's prescription is required.

The Hormone Cascade – Hierarchical Function

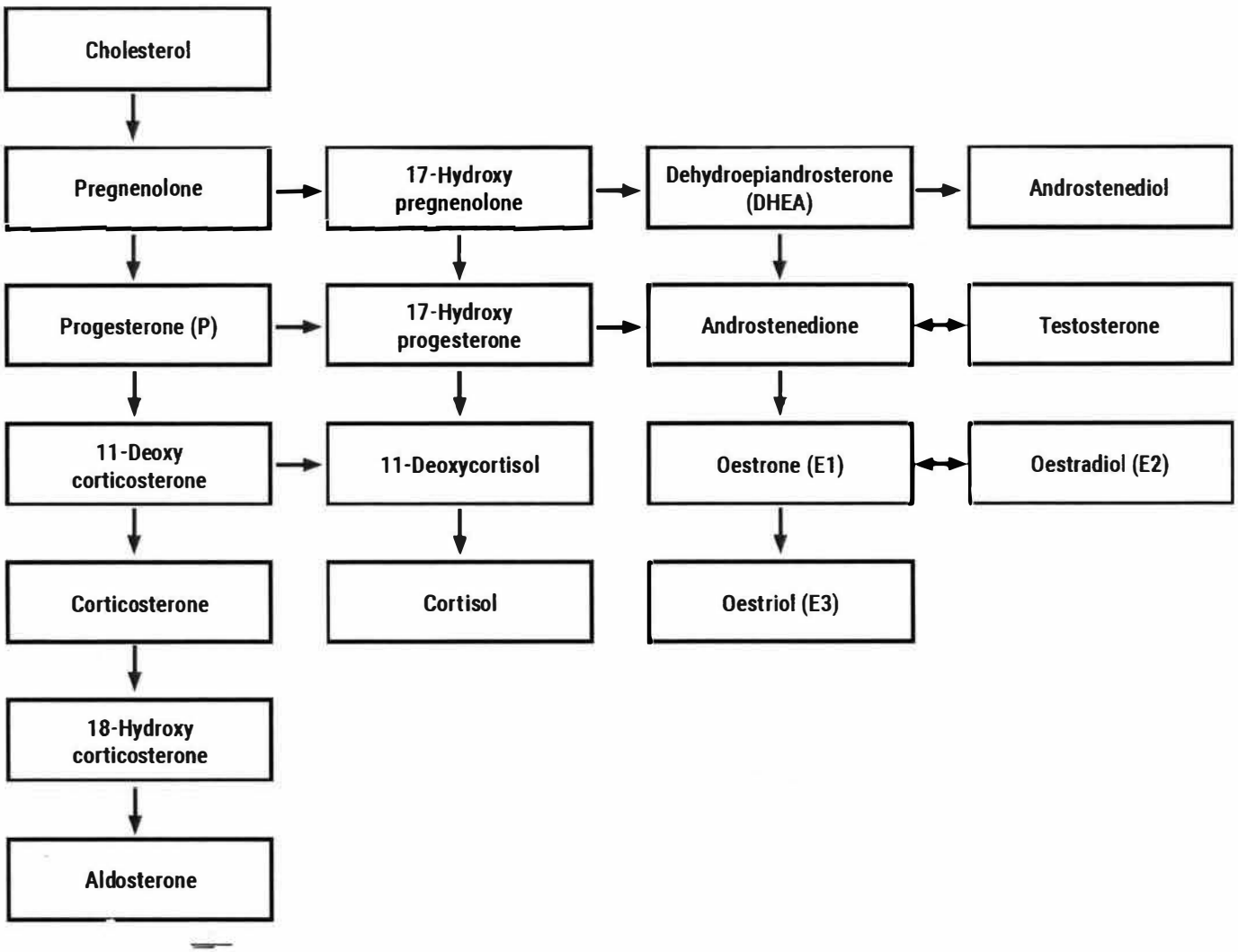
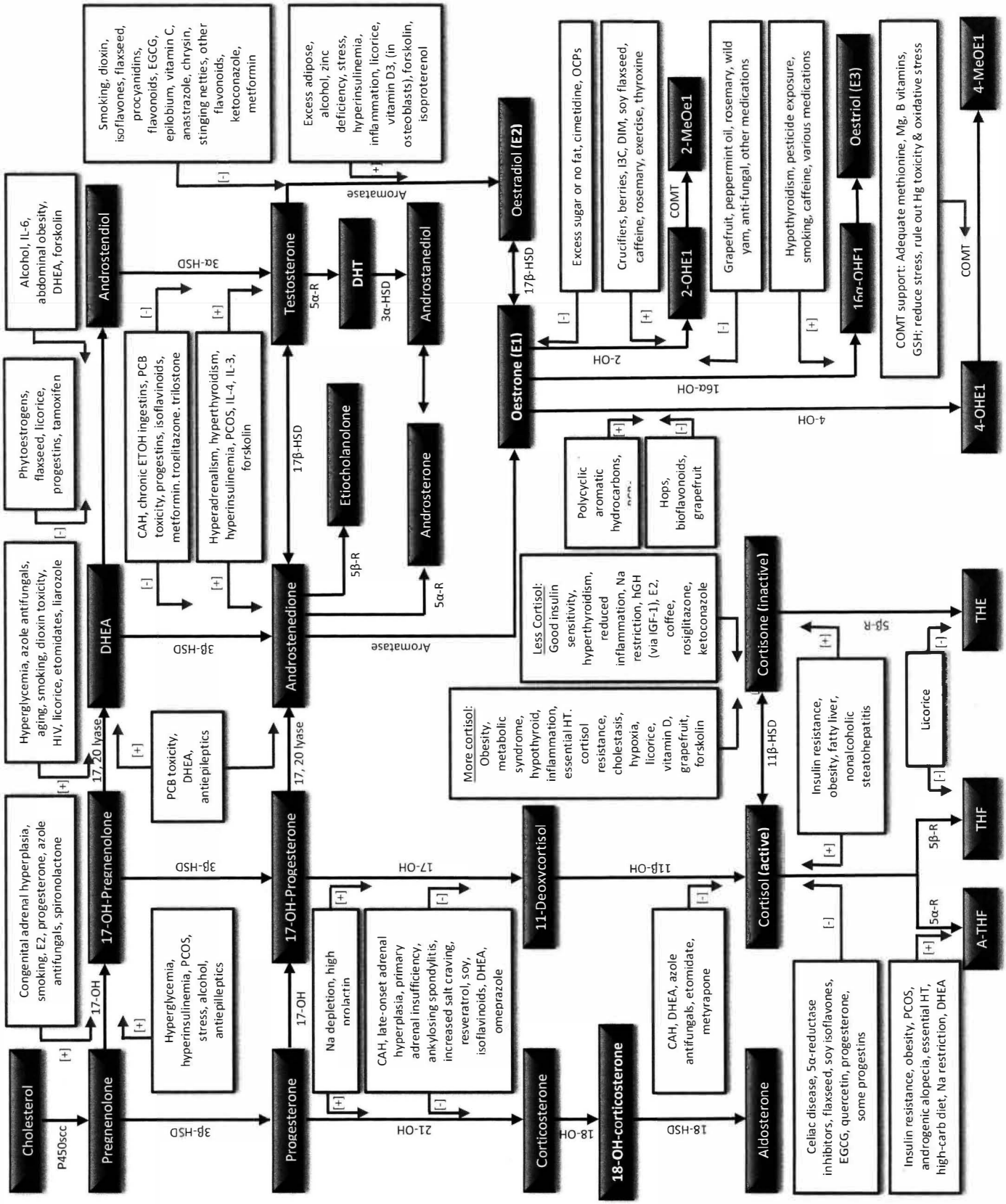


Figure 2. Hierarchical hormone cascade

All hormones originate from cholesterol and the enzyme pathway that is chosen will determine the end product. Pregnenolone, often referred to as the "mother of all hormones", has the potential to turn into almost any hormone. Depending on the local environment, the enzymes present, and the current bodily demands, certain pathways will be favoured over others. For example, the production of sex steroids is favoured in the gonads, with particular preference for oestrogen synthesis in the ovaries where aromatase levels are in abundance. Interestingly, during times of stress, cortisol synthesis will be favoured at the cost of reducing the synthesis and production of sex steroid hormones, highlighting ways in which dynamic demands on the body can sway the hormone cascade into one direction over another.

The Hormone Cascade – Influence of Exogenous Factors and Disease

Figure 3. Influence of exogenous factors and disease on the steroidogenic pathway (Adapted from Genova Diagnostics, 2007©)



The Endocrine Organs

The endocrine system is made up of a number of glands that synthesise and secrete hormones into circulation. Once in circulation, hormones can travel to distal organs or glands in the body where they typically stimulate further hormonal release in a sort of feedforward fashion.

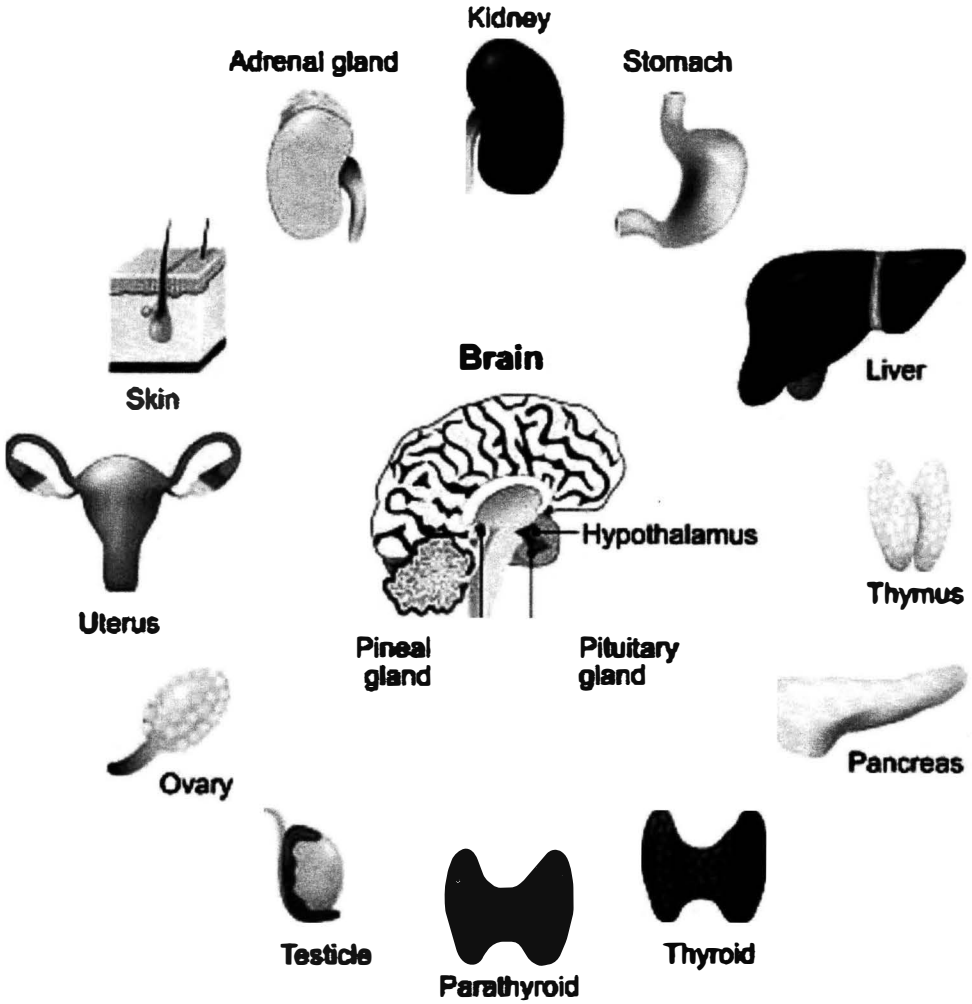


Figure 4. The endocrine organs.

The Menstrual Cycle Phases

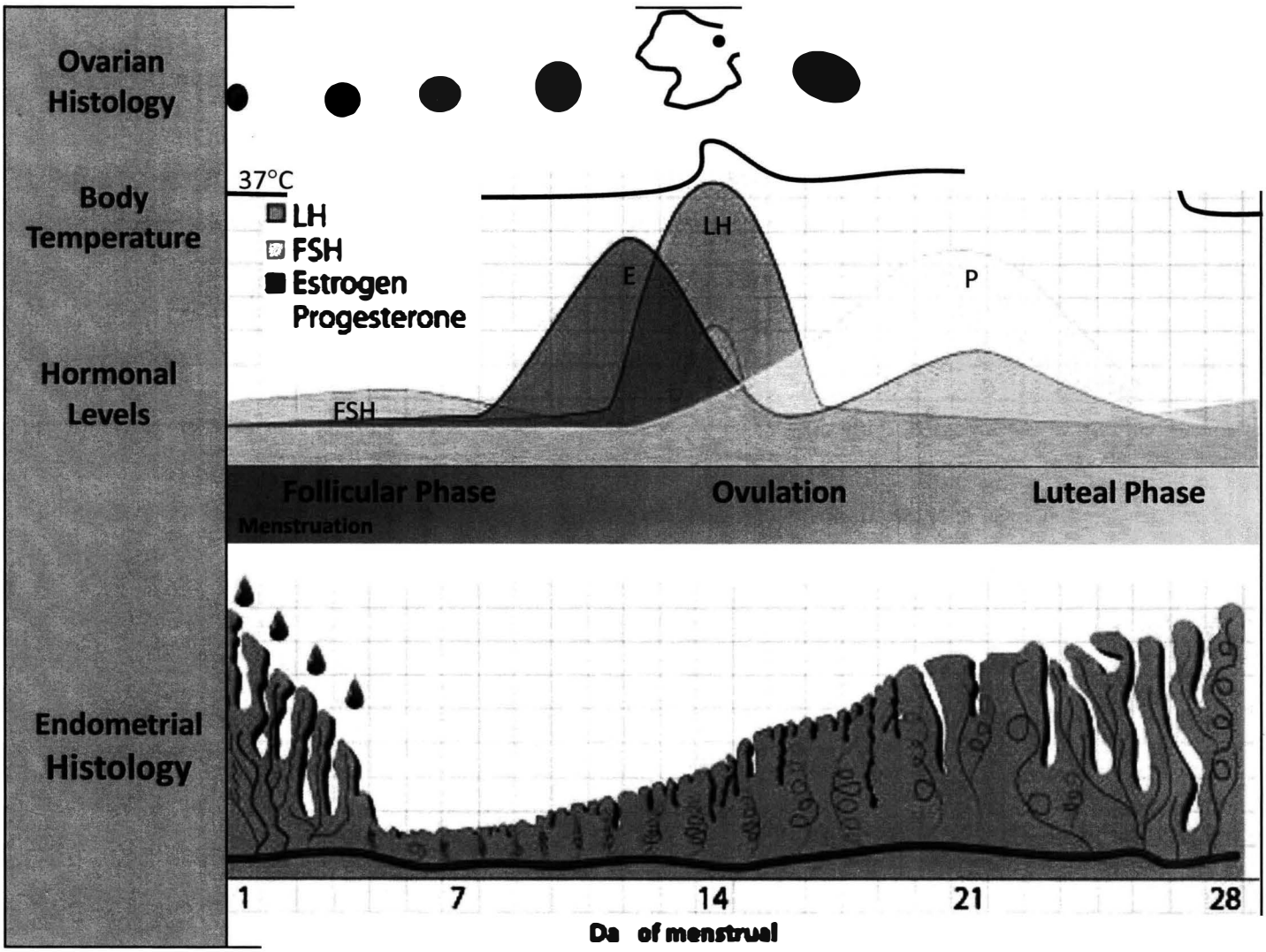


Figure 6. The menstrual cycle

The Menstrual Cycle Hormones

Luteinizing Hormone (LH)

- LH is synthesized and secreted by gonadotropic cells of the anterior pituitary.
- In females, LH marks the onset of ovulation and is responsible for the development of the corpus luteum, which in turn secretes progesterone.
- In males, LH stimulates testosterone production from leydig cells in the testes.

Follicular Stimulating Hormone (FSH)

- FSH is synthesized and secreted by gonadotropic cells of the anterior pituitary.
- In females, FSH stimulates the growth and maturation of an oocyte into an ovum.
- In males, FSH stimulates sperm production.

Oestrogen (E)

There are three types of endogenous oestrogens:

- Oestradiol: 95% of circulating oestradiol levels come from the developing follicle. Oestradiol is the more potent oestrogen produced by the ovary.

- Oestrone: The predominant form of oestrogen after menopause. Oestrone is produced by peripheral conversion of androstenedione in muscle and adipose tissue.

- Oestriol: A metabolic product of oestrone and regarded as a weaker oestrogen.

Oestrogens are involved in a number of processes and functions:

- Maintains bone density
- Increases metabolic rate
- Improves insulin sensitivity
- Regulates body temperature
- Prevents muscle damage / maintains muscle
- Improves sleep, mood, and concentration
- Increases blood flow
- Dilates small arteries, inhibits platelet stickiness
- Maintains collagen in the skin
- Decreases blood pressure
- Maintains memory and fine motor skills
- Decreases lipoprotein A, LDL, homocysteine,
- Increases HDL

Progesterone (P)

- Progesterone is synthesized and released primarily by the corpus luteum after ovulation
- A small amount is synthesized and secreted by the adrenal gland
- Essential for proper functioning of the cervix, uterus, endometrium, fallopian tubes, the CNS, the pituitary, and breast.
- Progesterone is considered a diuretic (mineralocorticoid receptor stimulation) and a sleep aid.

Sally's Daughter, Brittany, is Suffering from an Irregularity...

You first meet Sally the soccer mom when she brings in her 16-year-old daughter Brittany. Brittany is playing varsity soccer, and is already being recruited by prestigious colleges. She started her periods at age 14 ½ and has been having sporadic periods now. They last 3-5 days, but occasionally can be very heavy, causing her to miss school and sometimes important games. Her mother also shares that she can be pretty moody. Brittany complains also of bloating and acne. Her paediatrician wanted to put her on oral contraceptives, but that made her moods much worse, and gave her headaches. What does this suggest?

Group Discussion / Interactive Learning:

- Assess the situation.
- Apply the fundamental principles and rules of engagement for hormone therapy.
- Determine what tests might need to be performed.
- Determine an appropriate course of treatment.
- Provide an argument for Brittany and her doctor convincing them you are on the right path.
- Everyone contribute to the group discussion.

↓ Progest - heavy bleeding

Sally is in a Stage of Perimenopause...

You next see Sally a few years later when she presents as a patient herself. She had been dealing with irregular cycles the last few years. Sometimes they were as close together as 21 days, and other times she skips the month all together. Her biggest complaint was the disruption of her sleep. She has trouble falling asleep and occasionally has night sweats. Her second complaint is weight gain and bloating. She relates that she has gone up a pant size despite her normal rigorous exercise routine. She saw her gynaecologist who checked an FSH (which was 14) and told her she was not in menopause and to try oral contraceptives. After taking them for two months, she actually felt much worse. The bleeding was lighter and regulated but her night sweats were so much worse as was her breast tenderness. She presents to you for consultation.

Group Discussion / Interactive Learning:

- Assess the situation.
- Apply the fundamental principles and rules of engagement for hormone therapy.
- Determine what tests might need to be performed and what might be incorrect with the current treatment plan
- Suggest and alternative treatment plan.
- Everyone contribute to the group discussion.

SECTION III: Evaluating the Risks of Female Hormone Restoration

Sally and Susie in a State of Disrepair....

Sally presents for her follow up visit a year later and although her periods are still irregular, she is feeling much better. She is continuing to take her progesterone cream as you have prescribed. She relates that she is considering stopping the cream since her sister Susie recently got diagnosed with breast cancer. Sally heard that taking hormones could cause breast cancer and she does not want to increase her risk.

You suggest that Sally bring her sister, Susie, in for a consultation. Susie is her older sister and is 47-years-old. Her periods are still normal and going strong. She is a pharmaceutical sales rep for conjugated equine oestrogens and has a large territory, which involves a lot of travel. She is 5"2' (157 cm) and weighs 250 lbs (113 kg). She denies hot flashes but does admit to some bloating and PMS. She states that her job is stressful due to the recent drop in sales and a merger of her company. She is forced to eat on the run a lot and rarely has time for breakfast. She often has programs at night that include a late dinner. After obtaining notes from her surgeon, you learn that she was actually diagnosed with ductal carcinoma in situ, a precursor to breast cancer. Her doctor feels the lumpectomy resected all the abnormal cells, and forbids her from taking any hormones, including the oral contraceptives she was taking for the last 10 years. She has tried to lose weight but has been unsuccessful. She is willing to take any advice you have.

Group Discussion / Interactive Learning:

- Assess the situation.
- Apply the fundamental principles and rules of engagement of hormone therapy.
- Determine what tests might need to be performed.
- Determine an appropriate course of treatment.
- Prepare an argument for Susie and her doctor convincing them you are on the right path.
- Everyone contribute to the group discussion.

Evidence-Based Medicine: Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *Jama*, *288*(3), 321-333.

Objective:

- Assessed the major health benefits and risks of oestrogen plus progestin in postmenopausal women with an intact uterus aged 50-79.

Method:

- Participants received oral conjugated equine oestrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d in one tablet (n = 8506) or placebo (n = 8102). Intended duration of study was 8.5 years

Results:

- After a 5.2 year follow-up, the data and safety monitoring board stopped the trial because the use of oral oestrogen plus progestin was significantly correlated with an increased risk for breast cancer, cardiovascular disease, stroke, and venous thromboembolisms.

Food for Thought:

- According to a 2013 Global Consensus Statement on Menopausal Hormone Therapy, oestrogen restoration therapy in postmenopausal woman has been widely shown to reduce the risk of cardiovascular. What is accounting for the adverse cardiovascular events referred to in the WHI study?
- Progestin is not the same a progesterone. There is accumulating data highlighting the differences between synthetic and bioidentical therapy, many of which proposes a negative role for progestins in health.
- The route of administration can significantly influence the effect a drug or hormone will have on the body. There is accumulating data stating differences between oral and transdermal hormone therapy.
- The association between hormone restoration therapy and adverse health event varies further with type of hormone used (e.g., oestradiol, oestriol, and oestrone), as well as the concentration and ratios in which they are used.
- In the grand scheme of things, how significant are these risks?
    - In the 2002 WHI study, for 10 000 women there were 7 heart attacks, 18 blood clots, 8 strokes, 8 breast cancers, 6 less cases or colon cancer, and 6 less hip fractures. 97.5% of women on treatment had no adverse events.
- Do the risks outweigh the benefits?

Synthetic versus Bioidentical

In response to the 2002 World Health Initiative (WHI) reports on increased risk for cardiovascular disease, stroke, venous thromboembolisms, and breast cancer in relation to oral oestrogen and progestin replacement therapy, there were rapid declines in conventional synthetic hormone therapy. In its wake prescriptions and consumer demands for **bioidentical hormone therapy** rapidly rose. Since that time there has been much debate pertaining to the safety of these natural alternatives. While proponents of bioidentical hormones advocate that they are safer relative to synthetic versions, the FDA states that there is minimal to no evidence supporting these claims. Although still in its infancy, empirical data pertaining to the safety and efficacy of bioidentical use is beginning to unravel (*for a review see* Holtorf, 2009).

Patient Satisfaction

Evidence-Based Medicine: Holtorf, K. (2009). The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine, 121*, 1-13.

In a review, four studies compared the efficacy, patient satisfaction, and quality of life of female patients switching from synthetic medroxyprogesterone (MPA) to bioidentical progesterone. In all 4 evaluations, patients reported greater satisfaction, fewer side effects, and improved quality of life upon switching to progesterone (Holtorf, 2009).

Breast Cancer Risk

Evidence-Based Medicine: Holtorf, K. (2009). The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine, 121*, 1-13.

With the WHI reports that synthetic progestins are associated with greater risk of breast cancer, much of the research on bioidentical safety has been in relation to breast cancer. In a study that evaluated breast cancer risk in over 50 000 postmenopausal women, synthetic progestins significantly increased the risk of breast cancer by a risk ratio of 1.4, while progesterone reduced the risk of breast cancer by a risk ratio of 0.9 (Fournier et al., 2005). In another report, oestrogen plus progestin increased breast cancer risk by 1.69, with no significant increases in risk when progesterone was used (Fournier et al., 2008). These opposing differences in breast cancer risk may, in part, be due to their different mechanisms of actions in breast tissue.

It is well established that synthetic progestins have potential anti-apoptotic effects that can significantly increase oestrogen-mediated cell growth and proliferation of breast tissue (Hissom et al., 1987; Kalkhoven et al., 1994; Ory et al., 2001; Satitoh et al., 2005; Wood et al., 2007). In addition, synthetic progestins have been shown to down-regulate oestrogen receptor-beta (whose activation is associated with breast cancer prevention) (Isaksson et al., 2002). Contrary to this, progesterone has been shown to inhibit oestrogen-mediated expression of oestrogen-receptor-alpha (whose expression is associated with breast cancer promotion) and has anti-proliferative effects in breast cancer tissue (Mohammed et al., 2015). Moreover, current data suggests that synthetic progestins may facilitate the conversion of weaker endogenous oestrogen into more potent oestrogens that can potentially increase the risk of developing breast cancer. For example, MPA facilitates the metabolism of inactive oestrone sulphate into active oestrone by increasing sulfatase activity (Xu et al., 2007); an effect that is not observed with progesterone. Interestingly, not only is this effect not seen with progesterone, progesterone actually stimulates the conversion of potent oestrogens into weaker oestrogens by activating 17-beta-hydroxysteroid dehydrogenase (Schmidt et al., 1998). Considering these findings it appears that synthetic progestins are associated with greater risk of breast cancer, while progesterone may even reduce the development of breast cancer.

Cardiovascular Risk

Evidence-Based Medicine: Holtorf, K. (2009). The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine, 121*, 1-13.

There is an abundance of data (clinical trials, observational studies, and meta-analyses) that oestrogen treatment alone in post-menopausal women decreases coronary heart disease (Global Consensus Statement on Menopausal Hormone Therapy, 2013). Thus, the increased cardiovascular risk noted in the WHI study is likely associated with progestin use.

Indeed, in a study assessing levels of high-density lipoprotein (HDL; a determinant of cardiovascular protection) in women receiving oestrogen combined with levonorgestrel, MPA, or progesterone, both synthetic hormones significantly reduced HDL levels. Specifically, levonorgestrel reduced HDL and HDL sub-fraction 2 levels by 18% and 28% respectively, MPA reduced HDL and HDL 2 sub-fraction levels by 8% and 17% respectively, and progesterone produced no significant reduction (Ottosson et al., 1985). The negative effects of progestins on cardiovascular risk is also highlighted in studies assessing coronary artery spasms and atherosclerotic plaque formation. In a study conducted on primates, oestrogen plus progesterone were found to protect against thromboxane-induced coronary artery spasms; an effect that was lost when MPA was given in place of progesterone (Minshall et al., 1998). In another study it was found that progesterone, but not MPA, inhibits the expression of vascular adhesion molecule-1 in human vascular endothelial cells (Otsuki et al., 2001). Thus, once again, progestin and progesterone exhibit opposing effects of risk for pathology.

Depression Risk

Evidence-Based Medicine: Skovlund, C. W., Mørch, L. S., Kessing, L. V., & Lidegaard, Ø. (2016). Association of hormonal contraception with depression. *JAMA psychiatry, 73*(11), 1154-1162.

In this 2016 publication, Skovlund and team sought to investigate the relation between different types of hormonal contraception and subsequent use of antidepressants and depression diagnoses. This nationwide cohort study assessed a total of 1,061,997 women living in Denmark, aged 15 to 34, from January 1st 2000 to December 2013.

Changes in the incidence of rate ratios (RR) for the first use of antidepressants were compared between nonusers and users of different hormonal contraception:

- Individuals using combined oral contraceptives had an increased incidence RR of 1.23 for first use of antidepressants.
- Individuals using progestogen-only pills had an increased incidence RR of 1.34 for first use of antidepressants.
- Individuals using norgestrolmin patches had an increased incidence RR of 2.0 for first use of antidepressants.
- Individuals using etonogestrel vaginal rings had an increased incidence RR of 1.6 for first use of antidepressants.
- Individuals using levonorgestrel intrauterine system had an increased incidence RR of 1.4 for first use of antidepressants.

The incidence of depression diagnoses were similar or slightly lower than the estimates found for use of antidepressants and the rates of depression and use of antidepressant were found to decrease with age. Taken together, these data suggest that there is a positive relation between hormonal contraceptive use and incidences of depression.

However, when you consider the aforemention incidence RRs, the increased use of antidepressants was significantly greater for individuals taking synthetic progestins (i.e., norgestrolmin, etonogestrel, and levonorgestrel) compared to individuals receiving bioidentical progesterone.

Oral versus Transdermal

Transdermal oestrogen administration is preferred in most situations. Indeed, there is an abundance of information supporting the notions that oral, but *not* transdermal, oestrogen replacement is associated with:

Increased activation of inflammatory pathways (Vongpatanasin et al., 2003)

Increased risk of venous thromboembolisms (Canonico et al., 2007; L'Hermite, 2013; Scarabin et al., 2003)

Negative cardiovascular effects including stroke and hypertension (Schmidt & John, 2006; Strandberg et al., 2003)

Greater serum levels of oestrone (Scarabin et al., 2003). Reason being that oral oestradiol is metabolised to oestrone sulphate in the gut leading to supra-physiologic amounts of oestrone metabolites. Indeed an oral dose of 1.5 mg/day can result in oestradiol and oestrone excretion levels that are 3 and 10 folds higher than normal excretory levels, respectively. Given that most woman are able to sufficiently synthesize enough oestrone, and that oestrone is a potent oestrogen with the potential to exert damaging effect at high concentrations, increases in oestrone is not warranted.

Greater risk of developing breast cancer (Optamy et al., 2008; Schmidt & John, 2006)

Disruptions in tryptophan and serotonin metabolism, which can contribute to increases in depressive symptoms

Similarly, transdermal progesterone is over oral routes of administration. This is most notably due to the fact that transdermal delivery by-passes first-pass metabolism. Indeed, over 90% of oral progesterone is deactivated by enzymatic degradation in the gut and liver, significantly reducing its bioavailable-potential (Elshafie, 2007). While first-pass metabolism does occur at the level of the epidermis, it only accounts for 10% of that which takes place at the liver, rendering it an ideal alternative when first-pass needs to be avoided/reduced (Hotchkiss, 1998).

Evidence-Based Medicine: Canonico, M., Plu-Bureau, G., Lowe, G.D.O., & Scarabin, P.I. (2008). Hormone replacement therapy and risk of venous thromboembolism in a postmenopausal women: systematic review and meta-analysis. *British Medical Journal, 336,* 1227-1231.

Objective:

- Assessed the risk of venous thromboembolism in relation to hormone therapy.

Method:

- Meta-analysis of 8 observational studies and 9 randomized controlled trials

Results:

- Oral oestrogen but not transdermal oestrogen increased the risk of venous thromboembolism with an odds ratio of 2.5 and 1.2 respectively.
- Oral oestrogen but nor transdermal oestrogen increases plasma concentrations of prothrombin fragments 1 and 2 (marker for thrombin production).
- Unopposed oral oestrogen and opposed oral oestrogen produced no noticeable difference in the risk of venous thromboembolism

Oestrogen Types, Binding, and Dosing

There are three types of endogenous oestrogens:

- Oestradiol: The most potent oestrogen produced by the ovary.
- Oestrone: Potent and predominant form of oestrogen after menopause.
- Oestriol: A metabolic product of oestrone and regarded as a weaker oestrogen.

Binding Affinities and Receptor Distribution

Evidence-Based Medicine: Boothby, L.A., Doering, P.L., & Kipersztok, S. (2004). Bioidentical hormone therapy: a review. *Menopause, 11,* 356-367.

Oestrogens vary significantly in their binding affinities to oestrogen receptor-alpha and -beta. These variations in oestrogen binding affinity substantially influences the type and extent of effect these hormones produce. For example, in terms of breast cancer, activation of oestrogen receptor-alpha is associated with breast cell proliferation, while activation of oestrogen receptor-beta prevents breast cancer development (Paruthiyil et al., 2004). Moreover, alpha and beta oestrogen receptors vary greatly in their distribution throughout the body. Specifically, oestrogen receptor-alpha is located mostly in breast cancer cells, the endometrium, and ovarian stroma cells. Whereas oestrogen receptor-beta is located predominately in bone tissue, the brain, endothelia cells, intestinal mucosa, kidneys, lung parenchyma, and the prostate gland (Boothby et al., 2004.

The Binding Affinities for Oestrogen Receptor Alpha and Beta

	Oestrogen Receptor Alpha	Oestrogen Receptor Beta
17-beta-oestradiol	100	100
17-alpha-oestradiol	58	11
Oestriol	14	21
Oestrone	60	37
4-OH-oestradiol	13	7
2-OH-oestrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16
Genistein	4	87
Coumestrol	20	140

Table adapted from Boothby et al., 2004

When giving oestrogen, the ratio of the different types of oestrogens (i.e., oestriol, oestrone, and oestradiol) used is of important consideration. Notably, if weak oestriol is co-administered with potent oestradiol, oestriol can protect breast tissue from over-stimulation of oestrogen receptors (Holtorf, 2009; Melamed et al., 1997). Reason being, that oestriol competes with oestradiol for activation of oestrogen receptors. Given that oestriol is a much weaker oestrogen than oestradiol, its residence on oestrogen receptors in place of oestradiol lessens the oestrogen burden. Thus, in a way, oestriol acts as an anti-oestrogen.

Tri-est versus Bi-est

- Used to mimic a physiologic dosage of 80 : 10 : 10
- The oestrone is now thought to be unnecessary
- The body can convert oestradiol into the form that is needed
- Can vary concentration of Biest to 60 : 40 or 50 : 50
- Aim for less than 250ug oestradiol / day in combination
- Start low, go slow
- Dose with four days off each month
- May need to prime; (i.e., use a higher dosage for two weeks, then decrease the dose)
- Older women with very low levels of oestrogen may need a little oestrogen in order to respond to progesterone

Androgen Therapy

Evidence-Based Medicine: Labrie, F. (2007). Drug Insight: Breast cancer prevention and tissue-targeted hormone replacement therapy. *Nature Clinical Practice: Endocrinology & Metabolism, 3,* 584-593.

- After menopause, the adrenal glands become the predominant source of sex steroids through the production of precursor hormone, DHEA. However, by menopause serum DHEA levels have reduced by approximately 60% to that of levels seen in women 30 years and younger.

- Androgens are negatively correlated with breast cancer development. In fact, women with high androgen levels experience atrophy of breast tissue. In vitro evidence further supports this relation where both androgens and DHEA serve to inhibit oestrogen-stimulated breast cell proliferation. Moreover, unlike SERMs which are widely used for their antiestrogenic properties in breast tissue, DHEA offers further benefits by promoting bone formation.

Evidence-Based Medicine: Tamini, et al. (2006). Combined oestrogen and testosterone use and risk of breast cancer in postmenopausal women. *Archives of Internal Medicine, 166,* 1483-1489.

Objective:

- There exists contradictory data regarding the influence of androgens on breast cancer risk.
- The aim of this study was to evaluate the relation between oestrogen and testosterone use and breast cancer risk.

Method:

- 24 year follow-up of Nurses' Health Study assessing the breast cancer risk in postmenopausal women receiving different HRT formulations containing testosterone was performed.

Results:

- Postmenopausal women receiving oestrogen plus testosterone had a 2.5-fold increase risk of developing breast cancer than women who did not receive HRT.

- Breast cancer risk was significantly greater for women receiving oestrogen plus testosterone versus women receiving oestrogen-alone.

SECTION IV: Subjective and Objective Testing

Depression and Symptom Bias

If treatment range is influenced by subjective level of severity scores as concluded by a patient, then it would be beneficial to assess psychological and clinical depression separately from all other symptoms. We have provided you with one of many types of self-rating depression assessment scales as an aid to ruling out clinical depression (Zung et al., 1965).

Zung Self-rating Depression Scale (SDS) Checkmark ✓ the correct column as you feel since the last several days	Not at all or a little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down-hearted and blue.	1	2	3	4
2. Morning is when I feel the best.	4	3	2	1
3. I have crying spells or feel like it.	1	2	3	4
4. I have trouble sleeping at night.	1	2	3	4
5. I eat as much as I used to.	4	3	2	1
6. I still enjoy sex.	4	3	2	1
7. I notice that I am losing weight.	1	2	3	4
8. I have trouble with constipation.	1	2	3	4
9. My heart beats faster than usual.	1	2	3	4
10. I get tired for no reason.	1	2	3	4
11. My mind is as clear as it used to be.	4	3	2	1
12. I find it easy to do the things I used to.	4	3	2	1
13. I am restless and can't keep still.	1	2	3	4
14. I feel hopeful about the future.	4	3	2	1
15. I am more irritable than usual.	1	2	3	4
16. I find it easy to make decisions.	4	3	2	1
17. I feel that I am useful and needed.	4	3	2	1
18. My life is pretty full.	4	3	2	1
19. I feel that others would be better off if I were dead.	1	2	3	4
20. I still enjoy the things I used to do.	4	3	2	1
Tally				
Total =				

Table adapted from Zung et al., 1965

RESULTS:

☐ 25-49 Normal Range

☐ 50-59 Mildly Depressed

☐ 60-69 Moderately Depressed

☐ 70 and above Severely Depressed

Assessment Algorithm

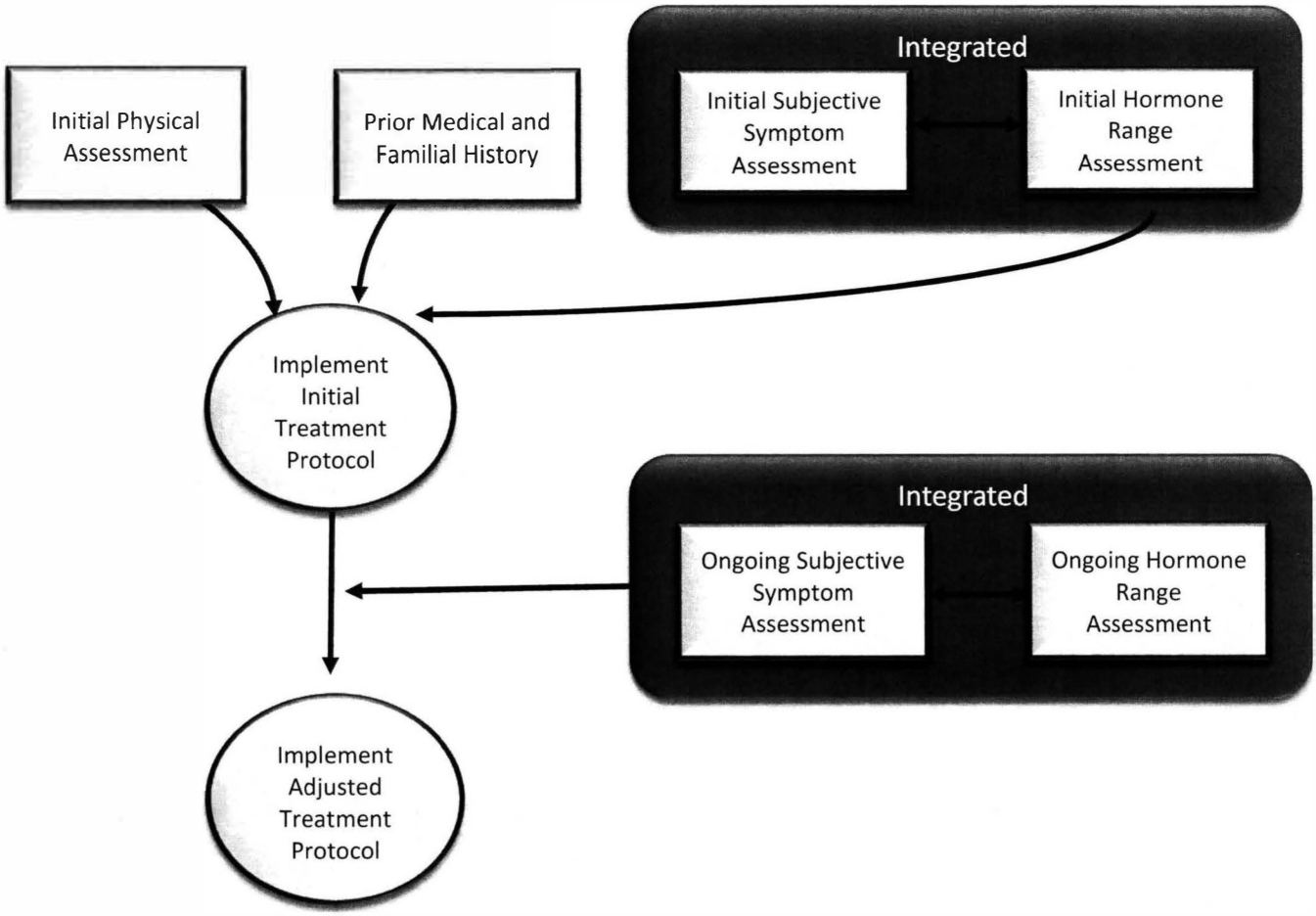


Figure 7. Assessment Algorithm. This is a suggested algorithm for the diagnosis and treatment of endocrine conditions. It is important to note that there may be different approaches in the diagnosis and treatment of hormonal conditions.

Ongoing Monitoring Chart <Template>

Symptoms	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Acne																														
Anxiety / Nervousness																														
Breast Tenderness																														
Cold Body Temperature																														
Confusion																														
Cramping Abdominal																														
Cravings for Sweet																														
Decreased Concentration																														
Decreased Sex Drive																														
Decreased Sexual Sensation																														
Depressed Mood																														
Fibrocystic Breasts																														
Fluid Retention Abdomen																														
Fluid Retention Extremities																														
Headaches																														
Heart Palpitations																														
Heavy & Irregular Menses																														
Hoarseness																														
Hot Flashes																														
Increased Facial / Body Hair																														
Irritability																														
Mood Swings																														
Night Sweats																														
Painful Intercourse																														
Premenstrual Syndrome																														
Sleep Disturbances																														
Tearfulness																														
Urinary Incontinence																														
Vaginal Dryness																														
Weight Gain: Hips																														
Weight Gain: Waist																														

Test Selection Form

1. Suggest hormone-related tests using the Test Selection Form: Notwithstanding the inclusion of prior medical history, current medication, pertinent familial history, lifestyle assessment, and concomitant differential diagnoses, suggested hormone-related tests can be selected and their results corroborated by signs and symptoms.

    - Suggested timeframe for hormone-related serum and saliva testing is mid-luteal phase of menstrual cycle.

    - If mid-luteal phase cannot be established, then start with serum testing, thyroid tests and metabolic labs along with FSH, LH, progesterone and oestradiol. Results of these tests can designate what part of the menstrual cycle the patient is in; follicular, mid cycle, or luteal. Derive the date when salivary testing is appropriate by counting forward from the day blood was drawn to identify mid-luteal phase.

Test Selection Form <Template>

TEST RESULTS						
	TEST TYPE	SOURCE	RESULT	L – N – H	RANGE	UNITS
o	**17-OH Progesterone**					
o	*Males*	Blood			1.8 – 10.4	nmol/L
o	*Females (Follicular phase)*	Blood			<3.3	nmol/L
o	*Females (Luteal phase)*	Blood			2.9 – 15.1	nmol/L
o	**25-OH Vitamin D**	Blood			50 – 150	nmol/L
o	**Androstenedione**					
o	*Female* (>18 yrs)	Blood			1 – 11.5	nmol/L
o	*Male* (>18 yrs)	Blood			2.1 – 10.8	nmol/L
o	**Cortisol**					
o	*Random*	Blood			70 - 550	nmol/L
o	*Morning*	Blood			110 - 550	nmol/L
o	*Evening*	Blood			70 – 400	nmol/L
o	*Morning*	Saliva			3.9 – 13.5	umol/L
o	*Midday*	Saliva			1.2 – 4.8	umol/L
o	*Evening*	Saliva			0.5 – 3.7	umol/L
o	*Night*	Saliva			0.3 – 2	umol/L
o	**DHEA**	Saliva			0.3 – 1.8	nmol/L
o	**DHEAS**					
o	*Female (15 – 20 yrs)*	Blood			5.2 – 7.5	umol/L
o	*Female (21 – 24 yrs)*	Blood			2.5 – 9.6	umol/L
o	*Female (25 – 34 yrs)*	Blood			1.4 – 8.7	umol/L
o	*Female (35 – 44 yrs)*	Blood			1.8 – 7.8	umol/L
o	*Female (45 – 55 yrs)*	Blood			0.7 – 5.4	umol/L
o	*Female (>56 yrs)*	Blood			0.8 – 3.2	umol/L
o	*Male (15 – 20 yrs)*	Blood			5.3 – 8.5	umol/L
o	*Male (21 – 24 yrs)*	Blood			3.7 – 10.2	umol/L
o	*Male (25 – 34 yrs)*	Blood			4.8 – 13.9	umol/L
o	*Male (35 – 44 yrs)*	Blood			2.2 – 12.4	umol/L
o	*Male (45 – 55 yrs)*	Blood			1.9 – 11.5	umol/L
o	*Male (>56 yrs)*	Blood			0.9 – 5.9	umol/L
o	**Dihydrotestosterone** (*Male*)	Blood			0.4 – 2.5	nmol/L
o	**Oestradiol (E2)**					
o	*Male*	Blood			<150	pmol/L
o	*Female (Follicular phase)*	Blood			70 – 130	pmol/L
o	*Female (Midcycle peak)*	Blood			230 – 1300	pmol/L
o	*Female (Luteal phase)*	Blood			200 – 790	pmol/L
o	*Female (Postmenopausal)*	Blood			<121	pmol/L
o	*Male*	Saliva			<8	pmol/L
o	*Female (Follicular phase)*	Saliva			2 – 8	pmol/L
o	*Female (Luteal phase)*	Saliva			6 – 17	pmol/L
o	*Female (Postmenopausal)*	Saliva			2 – 7	pmol/L
o	**Oestriol (E3)**					
o	*Male*	Saliva			3.5 – 20	pmol/L
o	*Female (Follicular phase)*	Saliva			3.5 – 98	pmol/L
o	*Female (Luteal phase)*	Saliva			3.5 – 98	pmol/L
o	*Female (Postmenopausal)*	Saliva			3.5 – 24	pmol/L
o	**Oestrone (E1)**					
o	*Male*	Saliva			39 – 58	pmol/L
o	*Female (Follicular phase)*	Saliva			43 – 64	pmol/L
o	*Female (Luteal phase)*	Saliva			39 – 58	pmol/L
o	*Female (Postmenopausal)*	Saliva			39 – 58	pmol/L
o	**FAI** (free androgen index)					
o	*Female (Premenopausal)*	Blood			0.3 – 9.8	
o	*Female (Postmenopausal)*	Blood			0.2 – 6.0	
o	**Ferritin**					
o	*Male (<15 years)*	Blood			20 – 250	ug/L
o	*Female (15 – 50 yrs)*	Blood			10 – 120	ug/L
o	*Female (>50 yrs)*	Blood			15 – 220	ug/L

o	**FSH**					
o	*Male*	Blood			1 – 8	IU/L
o	*Female (Follicular phase)*	Blood			4 – 16	IU/L
o	*Female (Midcycle peak)*	Blood			8 – 30	IU/L
o	*Female (Luteal phase)*	Blood			2 – 12	IU/L
o	*Female (Post-menopausal)*	Blood			>24	IU/L
o	**FT3**					
o	13 – 21 yrs	Blood			4.7 – 7.2	pmol/L
o	>21 yrs	Blood			3.5 – 6.5	pmol/L
o	**FT4**	Blood			9 – 25	pmol/L
o	**LH**					
o	*Male*	Blood			2 – 8	IU/L
o	*Female (Follicular phase)*	Blood			<16	IU/L
o	*Female (Midcycle phase)*	Blood			15 – 75	IU/L
o	*Female (Luteal phase)*	Blood			<16	IU/L
o	*Female (Postmenopausal)*	Blood			>24	IU/L
o	**Progesterone**					
o	*Male*	Blood			<5	nmol/L
o	*Female (Follicular phase)*	Blood			<6	nmol/L
o	*Female (Midcycle peak)*	Blood			>29	nmol/L
o	*Female (Luteal phase)*	Blood			10 – 70	nmol/L
o	*Female (Postmenopausal)*	Blood			<2	nmol/L
o	*Female (Follicular phase)*	Saliva			<5.0	nmol/L
o	*Female (Luteal phase)*	Saliva			10 – 70	nmol/L
o	*Female (Postmenopausal)*	Saliva			<1.0	nmol/L
o	**Prolactin**					
o	*Male*	Blood			45 – 375	mIU/L
o	*Female (Premenopausal)*	Blood			60 – 620	mIU/L
o	*Female (Postmenopausal)*	Blood			40 – 430	mIU/L
o	**PSA**					
o	<50 yrs	Blood			<2.6	ug/L
o	50 – 60 yrs	Blood			<3.6	ug/L
o	60 – 70 yrs	Blood			<4.6	ug/L
o	>70 yrs	Blood			<6.6	ug/L
o	**Quantitative HCG**					
o	*Male*	Blood			<5	IU/L
o	*Female* (pregnant)	Blood			>25	IU/L
o	**Reverse T3**	Blood			140 - 540	pmol/L
o	**SHBG**					
o	*Male*	Blood			15 – 50	nmol/L
o	*Female*	Blood			15 – 100	nmol/L
o	**Testosterone, Free**					
o	*Male*	Blood			200 – 600	pmol/L
o	*Female*	Blood			8 – 55	pmol/L
o	*Male*	Saliva			207 – 1173	pmol/L
o	*Female*	Saliva			25 – 473	pmol/L
o	**Testosterone, Total**					
o	*Male*	Blood			6 – 28	nmol/L
o	*Female*	Blood			0.4 – 2.1	nmol/L
o	**TPO Antibodies**	Blood			Negative	
o	**TSH** (*>2 yrs*)	Blood			0.5 – 5.0	mIU/L
o	**HbA1c**	Blood			<6.2 (Normal); >6.5 (Diabetic)	%
o	**Insulin, Fasting**	Blood			2 – 10	mU/L
o	**Glucose, Fasting**	Blood			3.0 – 6.0	mmol/L
o	**Cholesterol**	Blood			<5.6	mmol/L
o	**Triglyceride**	Blood			<2.0	mmol/L
o	**HDL**	Blood			>1.0	mmol/L
o	**LDL**	Blood			<2.5	mmol/L

Rules of Engagement Form

1. Discuss the fundamental principles of hormone therapy and Rules of Engagement that were used to assess, diagnose, and treat the patient.

<Template>

	RULE	USE AND EXPLANATION
☐	**Restoration and Balance:** Ascribe to hormone treatments that restore deficiencies and bring balance to the homeostatic mechanism within the female or male reproductive life cycle.	
☐	**Relative versus Absolute:** Concurrently, assess absolute hormonal levels as well as their relative qualifiable and quantifiable relationships to one another.	
☐	**Balance and Relative Sensitivity:** Be aware of the innate differences between individuals as it applies to the sensitivity of the relative relationship between any two hormones.	
☐	**Free versus Bound:** Qualify and quantify bound and bio-available hormone levels on an ongoing and consistent basis.	
☐	**Up and Down Regulation:** Assess prescribed hormone levels in order to rationalize the potential impact on up and down receptor site regulatory mechanisms.	
☐	**Agonist, Antagonist and Synergistic Activity:** Consider the impact of opposed versus unopposed hormones, and their concomitant impact on cellular and tissue proliferation.	
☐	**Pharmacokinetic versus Pharmacodynamic Balance:** Provide adequate and equitable consideration for the impact of what a drug agent is doing to the body and what the body is doing to that same drug agent.	
☐	**Cyclic versus Continuous Dosing:** Determine the absolute and relative short- and long- term significance of cyclic versus continuous hormone administration.	
☐	**Routes of Delivery and Delivery Systems:** Project the rate of absorption and subsequent bioavailability from known and / or hypothesized partition and diffusion coefficient-related variables.	
☐	**Monitoring Frequency and Treatment Regimens:** Monitor and subsequently adjust treatment protocols to minimize the quantity of hormones delivered while attempting to maximize therapeutic effect and reduce or avoid completely the potential for long-term side effects.	
☐	**Minimum Dose for Maximum Effect:** Restore; Balance; Pattern; Adjust; and Minimize	

Treatment Protocol Form

1. Develop a Treatment Protocol

<Template>

TREATMENT PROTOCOL DEVELOPMENT FOR HORMONE RESTORATION AND BALANCE				
	CLASSIFICATION		**HORMONE THERAPY**	
○	Addison's Disease	○	Dehydroepiandrosterone (DHEA)	
○	Adrenal Dysfunction	○	Oestradiol	
○	Ammenorrhea / Oligomenorrhea	○	Oestriol	
○	Androgens - High	○	Oestrone	
○	Androgens - Low	○	Hydrocortisone	
○	Andropause	○	Levothyroxine sodium (T4)	
○	Cortisol - Low	○	Liothyronine sodium (T3)	
○	Cortisol - High	○	Melatonin	
○	Cushing's Disease	○	Pregnenolone	
○	Diabetes: ☐ Type 1 ☐ Type 2	○	Progesterone	
○	Erectile Dysfunction	○	Spironolactone	
○	Oestrogen / Progesterone Deficiency	○	Testosterone	
○	Oestrogen Dominance	○	Vitamin D3	
○	Hashimotos Thyroiditis	○	**SUPPLEMENTAL THERAPY**	
○	Hyperthyroid	○	Adrenal Vitamins / Adaptogens	
○	Hypoadrenia	○	Chromium	
○	Hypogonadism	○	CoEnzyme Q 10	
○	Hypometabolism	○	Diindole Methane	
○	Hypopituitarism	○	Ferrous glycinate	
○	Hypothyroid	○	Iodine	
○	Menopause	○	Magnesium	
○	Osteopenia	○	Methylsulphonylmethane (MSM)	
○	Osteoporosis	○	Phosphatidyl Serene	
○	Perimenopause	○	Selenium	
○	Polycystic Ovarian Syndrome	○	Vitamin B-12 (Cobalamin)	
○	Premenstrual Syndrome	○	Vitamin B-5 (Pantothenic acid)	
○	Prolactinoma	○	Vitamin B-6 (Pyridoxine)	
○	Testosterone - Low	○	Vitamin B-7 (Biotin)	
○	Vaginal Atrophy	○	Vitamin B-9 (Folic Acid)	
○	Vulvodynia	○	Vitamin C	
○		○	Vitamin E	
○		○	Zinc	
○		○		

Hormone Testing

There are three principal body fluids from which to source hormones and four test types. Each has its place in assessing and monitoring hormonal levels for both female and male patient populations.

Group Discussion / Interactive Learning:

- Instruction: In small groups, identify a single summary-type advantage and disadvantage for each type of fluid used to test for hormones.

Body Fluid	Advantage	Disadvantage
Blood	price, availability, # of tests	Pain, Location, Measures bound hormones
Saliva	Convenience / Sample timing	Cost / Dry mouth Unmonitored / contamination Can't measure as much
Urine	Good for metabolites	
Blood Spot	Whole blood correlates in tissues blood	Cost / painful

Group Discussion / Interactive Learning:

- Instruction: There are a number of reasons to test for hormones. In small groups and based on all you have learned up to this point, identify at least five reasons / situations to test for hormones:

1.
2.
3.
4.
5.

Serum Testing

Advantages:

- Has been the long-standing method of choice for assessing large protein analytes (e.g., immunoglobulins) or very stable steroid hormones. As such, it is the predominant and conventional method of choice (Melmed at al., 2015).
- Has a well-established reference ranges for many hormones (Melmed et al., 2015).
- Ideal for peptide hormones (e.g., FSH, T3, and T4) (Melmed et al., 2015).

Disadvantages:

- Has limited utility for the measurement of sex hormones (e.g., oestrogen and testosterone). Unable to easily distinguish between bound and free oestrogen and testosterone (Melmed et al., 2015).
- Progesterone has many metabolites that are not easily detected with serum analyses.
- Normal ranges are fairly large- ranges are geared to detect disease, not imbalances.
- Represents a snapshot in time. As such, it has to be measured at the appropriate time of the cycle and compared to the normal range for that specific time period (Brambilla et al., 2007; Plymate et al., 1989).
- Often provides limited clinically useful information.
- Can be difficult to measure at the correct time of day due to logistics.
- Often requires anti-coagulants which can interfere with analytical tests.

Salivary Testing

Advantages:

- Easy to collect, stress free, and non-invasive. Accessible to practitioners, such a naturopaths, who may be practicing in states or provinces where they are not licensed to order or draw blood for testing. With the ease of this assessment it can be taken at multiple times throughout the day or month, providing a well-rounded picture of the hormone profile.
- Measure of free, unbound hormones. As blood circulates around salivary glands, steroid hormones that are not bound to blood components (i.e., CBG, SHBG, and albumin) can freely diffuse through the cells of the salivary gland into the salivary ducts. As such, saliva hormone levels correlate well with unbound serum hormone levels (Malamud, 2011; Wood 2009).
- More accurate assessment of transdermal hormone applications. Serum hormone levels drawn after transdermal application are only going to rise once the tissue reservoirs are saturated and overflowing. Thus, serum testing after transdermal application often underestimates the hormone level. Indeed, it would take exceedingly high, non-physiologic doses to get the serum level to move up into the endogenous range, which could lead to excessive dosing if practitioners try to achieve serum therapeutic levels (Elshafie et al., 2007).

Disadvantages:

- Restricted to steroid hormones; peptide hormones (e.g., FSH, T3, T4) cannot be measured using saliva (Malamud, 2011; Wood, 2009)
- Unable to measure steroid hormone metabolites.
- Imposes restrictions on a number of potential confounding variables (i.e., eating, drinking, makeup use, and dental hygiene) (Wood, 2009). Indeed, reports have shown that micro-damage caused by brushing your teeth can result in elevated salivary levels of testosterone for hours after brushing, even in the absence of visible signs of damage (Granger et al., 2004). Results can be further affected by the presence of periodontal disease (e.g., Sjogren's Disease).
- Not as accurate for hormones given sublingually.
- Not accepted by all insurance carriers.
- Transdermal application of hormones results in supra-physiological saliva levels that are significantly higher than serum levels. This is particularly noteworthy with transdermal progesterone and testosterone (Lewis et al., 2002; O'Leary et al., 2000). Thus, you must have the appropriate normal ranges and implement the appropriate withdrawals of exogenous hormones before testing.
- Not common practice in Australia

Urinary Testing

Advantages:

- Non-invasive with a wide range of hormones able to be measured (Kuijper et al., 2006).
- Good estimation of total daily production (Hourd & Edwards, 1994; Kuijper et al., 2006).
- Most economical and reliable method for evaluating steroid hormone metabolites (Hirohata et al., 2013; Kovacs et al., 2000)

Disadvantages:

- Urinary tests are inconvenient; need to collect for 24 hr, which can be hard to do with work. As such they are less common than serum and salivary measures in clinical practice.
- Uncertainty regarding the completeness of the collection
- Normal ranges are too often wide.
- More reflective of metabolites - what is being excreted rather than what is bioavailable and being used by tissues (Hourd & Edwards, 1994; Kuijper et al., 2006).
- Not common practice in Australia.

Recommendations on when to use Blood, Blood Spot, Urine, and Saliva Hormone Testing for Different Situation or Circumstance	
Hormone	**Test Type: Situation or Circumstance**
Oestradiol [Female]	**Blood**: Determine endogenous production prior to treatment with a topical preparation being performed by a practitioner with limited knowledge of saliva testing.
Testosterone [Male]	**Saliva**: Patient is being anti-coagulated and venipuncture may present a problem.
DHEA [Female & Male]	**Urine**: Trying to determine level over 24 hour time period to determine adrenal reserve.
Progesterone [Female]	**Blood spot** performed on a pharmacy technician that compounds with progesterone. Progesterone will often indicate false elevations in saliva due to normal respirations.
Progesterone [Male]	Male being treated with topical progesterone to decrease DHT formation. Uses his fingers to apply topical which could contaminate blood spot during sample collection. Blood sample would not represent topical administration.
Cortisol [Female]	**Saliva**: Performed secondary to pre-venipuncture or lancing procedural anxiety that results in false cortisol elevation.
HDL & LDL [As it relates to HRT]	**Blood Spot**: Patient presents with signs and symptoms of metabolic syndrome and has large insurance annual deductible for blood testing. Blood spot a lower cost yet effective solution.
FSH & LH [Female]	**Blood Spot**: Patient's work schedule conflicts with labs hours and hormone collection needs to occur on or near ovulation. Blood spot collection occurs during the proper time and schedule.
SHBG (BONUS!!!)	**Blood Spot**: Female diabetic that is very accustomed to finger pricks from lancing devices elects to test via blood spot. SHBG can be an indicator of insulin resistance.

Point of Interest: Hormone Testing and Route of Delivery

"There is controversy about the beneficial effects of topical progesterone creams used by postmenopausal women. A major concern is that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium. However, antiproliferative effects on the endometrium have been demonstrated with progesterone creams when circulating levels of progesterone are low. Thus, effects of topical progesterone creams on the endometrium should not be based on serum progesterone levels, but on histologic examination of the endometrium. Despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams."

Percutaneous Administration of Progesterone: Blood Levels and Endometrial Protection
Stanczyk FZ; Paulson RJ; Roy S
Menopause, 12, 232-7 (2005)

- Instruction: As an open discussion, what is learned from this research studies?

Point of Interest: A Note of Caution Regarding Normative Databases

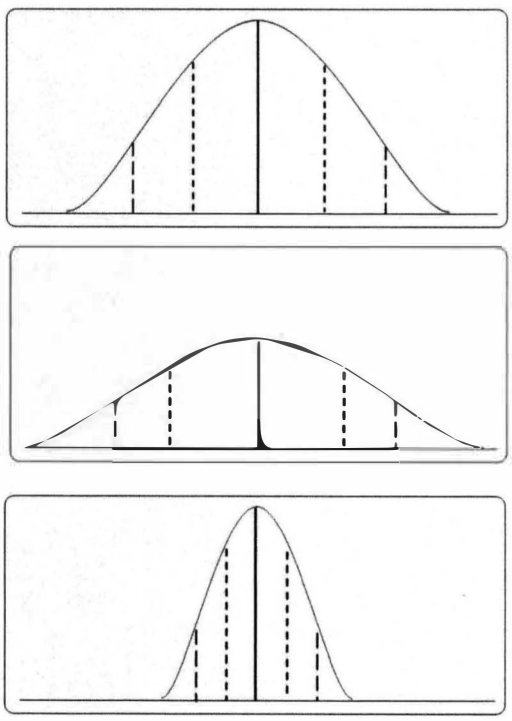
In hormone restoration and balance, normative data from body fluid-type test analyses require reference range data. Ideally, this data serves as a 'Gold Standard'. However, it is important to note that reference ranges may vary with age, sex, race, diet, and use of concomitant medications.

Reference ranges only denote the usual values in the population, and do not reflect that which is required for optimal health for the individual patient. This raises the issue, yet again, regarding philosophical approaches to hormone therapy. For example, the normative range values would vary for post-menopause and andropause patient populations depending on our goals and objectives.

Theoretically, standard reference ranges should not vary from one laboratory to another. This can be explained by the use of various analytical methods and the fact that results may be provided in differing units of measure. The fact of the matter is simply this; normative data from lab to lab does vary!

Particularly in the case of hormones, reference ranges vary greatly and are often relative in nature as opposed to absolute. In other words, they need be compared to other reference range data.

Laboratory test results should always be used in conjunction with other established diagnostic and / or treatment guidelines. It would be considered common practice and advisable to relate or formulate treatment protocols on a patient-specific basis based on test results and symptom assessment. Continually performing both assessments further assists in adjusting treatment protocols, always in the hope of refocusing on our 'moving target'!



SECTION V: Inter-Hormone Relationships

This entire section of the seminar addresses hormone deficiencies, imbalances, and inter-relationships between hormones. The following information is a strong example of the significance of inter-relationships between hormones and how we need to think when we examine deficiencies, imbalances, and subsequent treatment regimens.

Case in Point:

- Oestrogen induces the up-regulation of its own receptors, while progesterone can down-regulate oestrogen receptors in the breast.
- Oestrogen up-regulates progesterone receptors allowing progesterone to initiate its activities.
- In the absence of progesterone, oestrogen's proliferation on oestrogen sensitive tissue will increase.
- Progesterone in the absence of oestrogen can worsen glucose tolerance as well as worsen menopausal symptoms.
- Oestrogen can enhance cellular mitosis, whereas progesterone induces apoptosis thus preventing tissue overgrowth.
- Oestrogen stimulates the endometrium, while progesterone improves endometrial function
- Oestrogen restrains bone loss, while progesterone stimulates new bone formation

Oestrogen and progesterone sometimes act as antagonists. Their actions are designed to balance each other and keep each other in check. At no time do hormones act independently under normal circumstances in healthy bodies.

For example, oestrogen increases cell proliferation in the endometrium, while progesterone inhibits cell proliferation. Without progesterone, endometrial hyperplasia can occur in the uterus. Progesterone is synthesized primarily by the corpus luteum, the follicle transformed after ovulation, and also to a small degree by the adrenals. In the ovary, progesterone production is activated at ovulation, approximately 15 days before the next menstruation. This is stimulated by the release of luteinizing hormone from the pituitary gland. If fertilized this production of progesterone is crucial to the survival of the ovum. When pregnancy occurs, progesterone production rapidly increases and its synthesis is taken over by the placenta. If a woman does not get pregnant, the corpus luteum involutes and progesterone production diminishes and eventually disappears in parallel with oestrogen production, heralding menstruation.

Progesterone is a precursor to most sex hormones, including oestrogen in the ovaries, testosterone, all androgens, and other adrenal hormones, making it an extremely important hormone for reasons far beyond its role as a sex hormone. Progesterone in the breast and uterus counteracts the stimulation of cell growth, which is a direct action of oestrogen. It accomplishes this by activating the progesterone receptor, which in turn, down-regulates the oestrogen receptor. Because progesterone suppresses oestrogen-driven cell proliferation, progesterone in the natural state helps keep breast cell growth in healthy balance.

Group Discussion / Interactive Learning:

- Instruction: What rules are at play in the previous section?

RULES			
☐	Restoration and Balance	☐	Pharmacokinetic versus Pharmacodynamic Balance
☐	Relative versus Absolute	☐	Cyclic versus Continuous Dosing
☐	Balance and Relative Sensitivity	☐	Routes of Delivery and Delivery Systems
☐	Free versus Bound	☐	Monitoring Frequency and Treatment Regimens
☐	Up and Down Regulation	☐	Minimum Dose for Maximum Effect
☐	Agonist, Antagonist and Synergistic Activity		

Group Discussion / Interactive Learning:

- Instruction: In small groups, identify the relative relationship between the below set of hormones. Utilize the set of established rules to guide you through this process.

Examples of Relative Hormone Relationships

Hormone (1)	Hormone (2)	Relative Relationship
Insulin	DHEA	DHEA can improve insulin sensitivity.
Oestrogen	Progesterone	
Oestrogen	Testosterone	
Testosterone	DHEA	
Thyroid	Progesterone	

SECTION VI: Adrenal Function and Dysfunction

Sally has succumbed to Fatigue...

Sally comes in the next year for her check-up. Almost two years has passed since her husband Jake died. She feels better emotionally, but still is feeling financial stress. Although the children have all moved out of the house and are away at college, she is still upset about having to sell her home and downsize to a condo. She reports extreme fatigue that is worse in the morning. At times she can barely get out of bed. She no longer can meet her friends for their 6:00 am run. She complains of poor concentration and fogginess. She is most upset about her continued weight gain, especially in her abdomen. She feels best in the evening, and although she is tired at bedtime, she can't fall asleep. She is often up until 1:00 am, and tosses and turns most of the night. She denies hot flashes or night sweats. She also complains of palpitations, mostly at night. Her family doctor wanted to start her on an antidepressant, but she wants your opinion.

Group Discussion / Interactive Learning:

- Assess the situation.
- Apply the fundamental principles and rules of engagement for hormone therapy.
- Determine what tests might need to be performed.
- Determine an appropriate course of treatment.
- Everyone contribute to the discussion.

The Physiological Stress Response

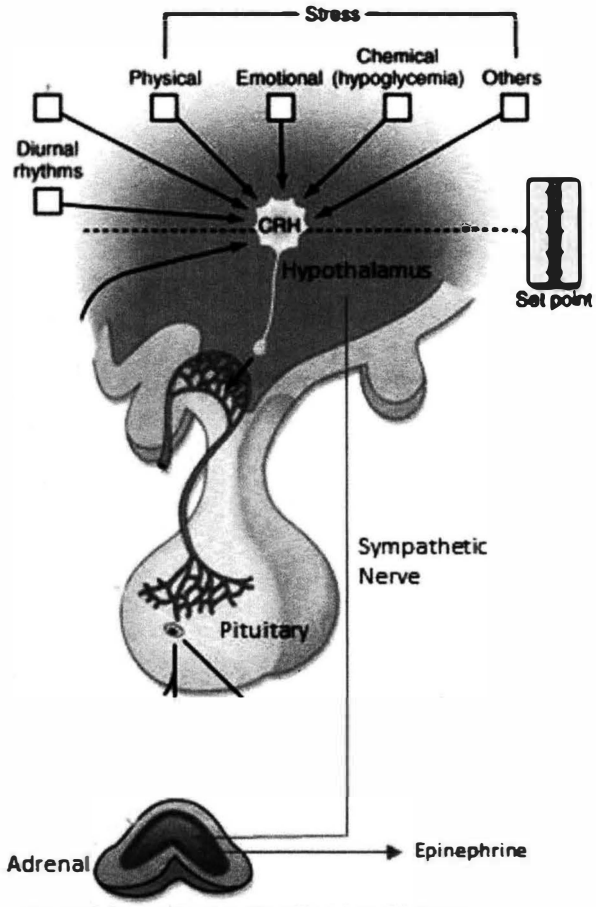


Figure 8. The Sympathetic-Adrenal-Medullary (SAM) Axis

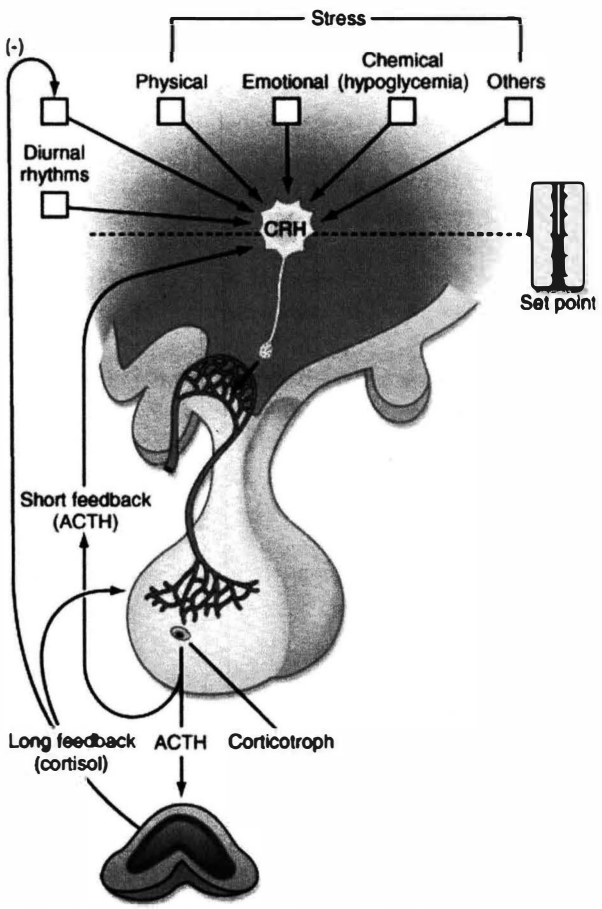


Figure 9. The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The stress response is a necessary and adaptive physiological response system that mobilizes the body to respond to intrinsic and extrinsic stressors (Melmed et al., 2015; Tsigos & Chousos, 2002). This intricate and well-coordinated system is necessary for ensuring survival of the species (i.e., food intake, sexual reproduction, maternity/paternity behaviour, avoidance of danger and threat, among much more) and is initiated and maintained by two systems:

- Sympathetic-adrenal-medullary (SAM) axis: Fast and quick response system
- Hypothalamic-pituitary-adrenal (HPA) axis: Slow and longer lasting response system

General Adaptation Model

Coined by Hans Selye in 1936 the General Adaptation Syndrome model outline three stages of the stress response (Selye, 2013):

Stage 1 – Alarm Reaction:

- The *alarm reaction* stage refers to the body's initial reaction to a perceived stressor, as interpreted by the hypothalamus, which is responsible for integrating intrinsic (e.g., deviations in homeostatic set points) and extrinsic (e.g., external threats) information. When a stress is perceived, the hypothalamus rapidly initiates and coordinates the stress response through the activation of the SAM and HPA axes.

- The **SAM axis** is the rapid and quick response system responsible for 'fight or flight' (e.g., why you jump/startle when there is a loud noise). In this system, the hypothalamus activates descending sympathetic efferent nerve fibers which innervate peripheral organs to stimulate changes adapted for stress (e.g., pupil dilation, increased HR, increased BP, etc.). These adaptive responses are further potentiated with the sympathetic activation of the adrenal medulla which causes the secretion of epinephrine/norepinephrine that further stimulate peripheral organs (Tsigos & Chousos, 2002).

- The **HPA axis** is the slower, but longer lasting response system that predominately functions to mobilize energy storages (i.e., fat reserves, protein reserves, and carbohydrate reserves) that provide fuel to keep up with the demands on the body during a stressful situation. This is achieved through the coordinated chain of communications between the hypothalamus, pituitary, and adrenal cortex that ultimately results in pronounced secretion of glucocorticoids (e.g., cortisol – the 'stress' hormone) (Tsigos & Shousos, 2002).

- Together, this stage of the stress response is characterized by significant increases in the synthesis and secretion of epinephrine/norepinephrine and cortisol. This shift in hormone synthesis is paired with drops in testosterone and DHEA levels.

Stage 2 – Resistance:

- During the *resistance* stage sympathetic arousal (i.e., SAM axis) subsides.

- HPA axis activity is maintained, cortisol levels remain elevated, and DHEA levels continue to drop. During this stage the body remains in a state of arousal as an adaptation to deal with potential lingering threats.

- Under adaptive circumstances, HPA activity is maintained acutely and shut-down by cortisol negative feedback onto the hypothalamus and pituitary. Failure to shut down HPA activity results in chronic arousal that can lead to a state of exhaustion.

Stage 3 – Exhaustion:

- The *exhaustion* stage of the stress response is a maladaptive response characterised by chronic activation of the HPA axis. Chronic activation of the HPA axis ensues with repeated exposure to stressors and mechanistic failures to shut-down this system.

- The sustained elevated cortisol levels over time can:
    - Destroy healthy muscle and bone
    - Slow down healing and normal cell regeneration
    - Impair digestion
    - Interfere with healthy endocrine function
    - Weaken the immune system
    - Compromise metabolism and add more weight around the middle

Cortisol

Cortisol produces wide-spread effects on the body with substantial influence over entire endocrine systems and physiological functions. For example, cortisol maintains blood pressure through aldosterone production (Toda et al., 2013). It also plays an important role at maintaining blood glucose levels during periods of stress by inducing gluconeogenesis and glycogenolysis (Cryer et al., 2003), and it has been shown to decrease bone mineralization and suppress immune system activity (Henneicke et al., 2014). In these examples alone, we see cortisol's wide-spread, whole body effects on cardiovascular output, glucose metabolism, bone mineralization, and immune reactivity. There is also an abundance of information describing cortisol's effect on the thyroid and consequently on the secretion of thyroid hormones.

Cortisol and thyroid hormones both need to be present in cells for optimal energy and metabolic activity. Indeed, many cells in the body have receptors for both cortisol and thyroid (Hollenberg, Giguere, Segui, & Evans, 1987). When cortisol levels are low, caused by adrenal fatigue, exhaustion, or Addison's disease, thyroid is less efficient at doing its job of increasing energy and metabolic activity (Melmed et al., 2015). Conversely, excessive cortisol secretion can desensitize cellular ability to respond to thyroid hormone stimulation, which can result in thyroid resistance. In this circumstance, thyroid hormone levels can be normal, but tissues fail to respond as efficiently to thyroid signal because of high cortisol levels (Duval et al., 2006).

Moreover, this desensitisation effect cortisol has on thyroid receptors extends to insulin receptors, progesterone receptors, testosterone receptors, and oestrogen receptors (Park & Ahima, 2015; Westpal, 1986). Consequently, insulin, progesterone, testosterone, and oestrogen are unable to sufficiently exert their actions and we see symptoms indicative of drops in these hormone levels, despite these hormone levels being normal. As such, there are many instances where these patients are placed on exogenous oestrogen/ progesterone / thyroid hormone / testosterone hormone therapy in attempts to normalize the symptoms. All the while, cortisol imbalance is the underlying cause.

Thus, considering cortisol's wide-spread effects, it should come to no surprise that cortisol is associated with a number of pathological conditions and symptom (*refer to table3)*.

Pathological Conditions Associated with Cortisol Imbalance

Low Cortisol	**High Cortisol**
End stage adrenal disease	Early stage adrenal disease
Adrenal Hyperplasia	Hypertension
Anovulation	Hypoglycaemia
Luteal phase defects	Hypothyroidism
Drug-induced adrenal suppression	Pituitary adenoma
Hypothyroidism	Pregnancy

Table adapted from: Bjorntorp & Rosmon, 2000; Manenschijn, 2013; Philips et al., 2013

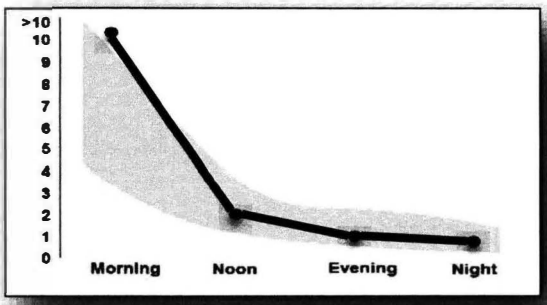
Specific Symptoms of Hormone Imbalances in Females

Increased Testosterone in Females	Decreased Testosterone in Females	
Acne	**Apathy**	Burned Out Feeling
Decreased Concentration	**Decreased Sex Drive**	Cold Extremities
Deepening of Voice	**Decreased Sexual Sensation**	Dry Eyes
Increased Facial and / or Body Hair	**Decreased Stamina**	Foggy Thinking
Increased Hair Loss	**Depressed Mood**	Headaches
Irritability	**Dry Skin / Hair**	Increased Facial and / or Body Hair
Mood Swings	**Fatigue**	Memory Problems
Weight Gain: Waist	**Joint Pains**	Painful Intercourse
	Muscle Pain	Tired But Wired
	Thinning Skin	Urinary Incontinence
		Vaginal Dryness

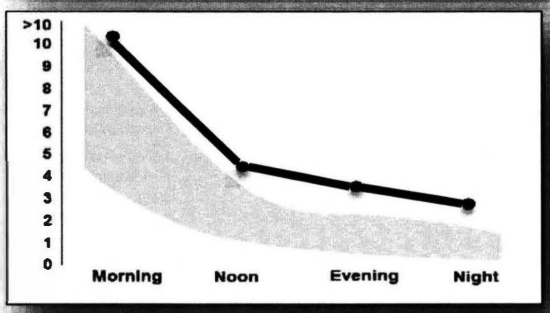
Increased DHEA in Females	Decreased DHEA in Females	
Acne	**Apathy**	Chemical Sensitivities
Anxiety / Nervousness	**Burned Out Feeling**	Decreased Concentration
Increased Hair Loss	**Decreased Sex Drive**	Memory Problems
Irritability	**Decreased Sexual Sensation**	Salt Craving
Deepening of Voice	**Decreased Stamina**	Thinning Skin
Weight Gain: Waist	**Depressed Mood**	
	Dry Skin / Hair	
	Fatigue	
	Joint Pains	
	Muscle Pain	
	Tired But Wired	

Increased Cortisol in Females	Decreased Cortisol in Females
Anxiety / Nervousness	
Decreased Concentration	
Fluid Retention Abdomen	
Fluid Retention Extremities	**Apathy**
Foggy Thinking	**Burned Out Feeling**
Heart Palpitations	**Chemical Sensitivities**
Hot Flashes	**Cold Body Temperature**
Hypoglycaemia	**Decreased Stamina**
Mood Swings	**Fatigue**
Sleep Disturbances	**Hypoglycaemia**
Tired But Wired	**Joint Pains**
Weight Gain: Waist	**Low Blood Pressure**
Confusion	**Salt Craving**
Decreased Sex Drive	Cold Extremities
Depressed Mood	Cravings for Sweet
Irritability	Muscle Pain
Memory Problems	
Night Sweats	
Thinning Skin	

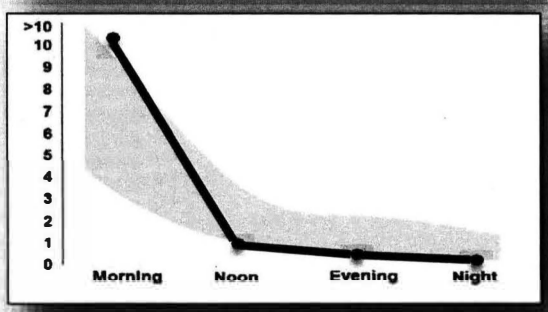
Cortisol Data Plots



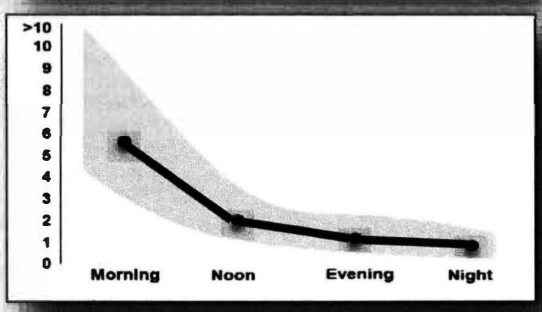
Normal. → High in AM.



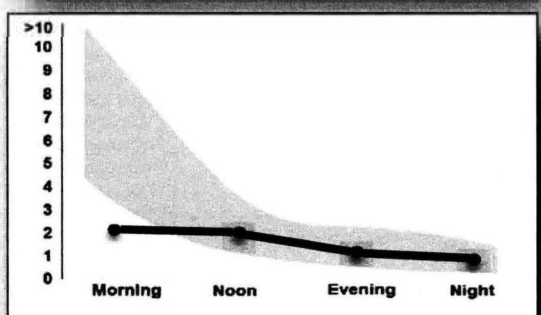
Stressed - check if patient has cushings
or
Fasting
or
Using ~~hydrocortisone~~ cream



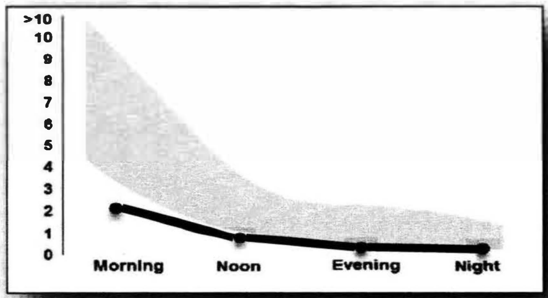
Low cortisol



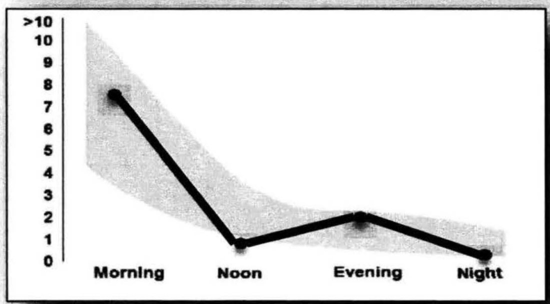
Progressing to later stages of Adrenal function.

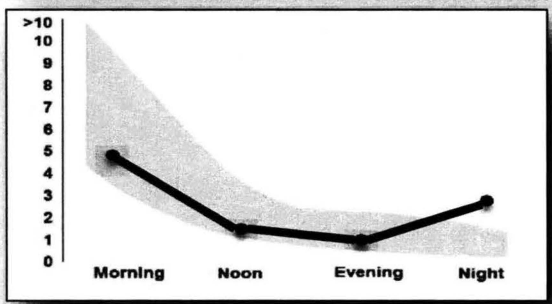


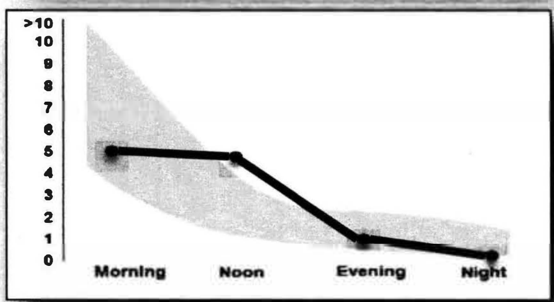
Low cortisol →

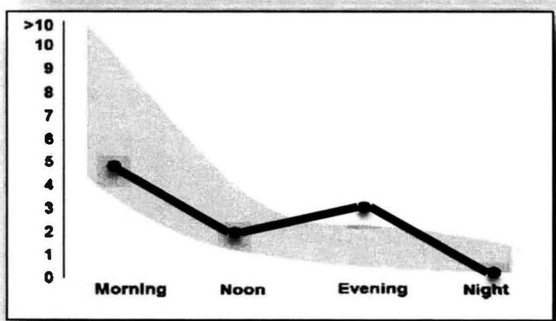


ACTH test - Maybe had Cortisol









Progesterone Steal

We see further evidence for cortisol's wide-spread effects on the body in terms of the hormone cascade and synthesis. When the HPA axis is chronically activated preference is made for cortisol synthesis in the adrenals. Consequently, pregnenolone and progesterone levels will eventually drop over time (Karalis et al., 1996). Under these circumstance pregnenolone and progesterone shunt away from the synthesis of aldosterone, DHEA, and testosterone in favour of cortisol production. With reductions in aldosterone secretion sodium and potassium imbalances emerge resulting in increased salt and water retention, salt cravings, and intolerance to banans (i.e., potassium).

Symptoms of progesterone steal:

- Excessive fatigue
- Nervousness/ irritability
- Depressed mood
- Inability to concentrate
- Apprehensions
- Weakness
- Feelings of frustration
- Cravings (salt and sugar)
- Vertigo
- Light headedness
- Insomnia
- Worsening PMS
- Headaches
- Muscle pains and spasms
- Epigastric pain
- Food and other allergies
- Dyspepsia-indigestion
- Diarrhoea-constipation

Typical energy patterns or progesterone steal:

- Morning fatigue; very hard to get up & get going
- Feels better until lunch
- Mid-afternoon crash; often craves carbs for energy
- Increase in energy after 6 pm
- Tired at 9-10 pm
- Second burst of energy if up at 11 pm, often lasting to 1-2 am
- Sleeps best in morning 7-9 am
- Often is most productive late at night

Low Androgens in Females

Reasons for low androgen levels in females include (Bachman et al., 2002):

- Surgical Menopause
- End stage adrenal fatigue
- Aging
- Isolated testosterone deficiency
- Obesity; excessive aromatase activity

Low androgen levels or symptoms of low androgens can result from various hormone imbalances, not just of the androgen class (Melmed et al., 2015; Westphal, 1986):

- Elevated cortisol secondary to stressors can have a dramatic effect upon female sexual desire.
- Elevated cortisol can diminish testosterone receptor activity.
- Elevated oestrogens can elevate SHBG leading to increased testosterone protein binding followed by decrease tissue receptor binding, and then a subsequent decrease in testosterone activity.
- Low androgens can stress the adrenal glands ability to synthesize DHEA.

High Androgens in Females

Reasons for high androgen levels in females include (Bachman et al., 2002):

- Anovulation
- Polycystic Ovary Syndrome (PCOS)
- Adrenal hyperplasia
- Early stage adrenal fatigue
- Genetic / constitutional
- Metabolic syndrome (Low SHBG)

High androgen levels or symptoms of high androgens can cause or create other hormone imbalances (Melmed et al., 2015; Westphal, 1986):

- Elevated cortisol can mimic many symptoms of testosterone excess.
- Elevated testosterone coupled with elevated cortisol can increase testosterone conversion to oestradiol through increased aromatase activity.
- Excess testosterone in peri- and post- menopausal women can worsen oestrogen dominance.

Point of Interest: Adrenal Fatigue

While Addison's disease (i.e., hypo-adrenal function) and Cushing's disease (i.e., hyper-adrenal function) are well established and well recognized disorders, the remaining spectrum of adrenal dysfunctions remain largely overlooked (Guilliams & Edwards, 2010). This is particularly the case with adrenal fatigue. Adrenal fatigue is defined as a subclinical condition/phenomenon characterized by insufficient secretion of adrenal hormones (Allen, 2013). Stated otherwise, adrenal fatigue describes the spectrum of adrenal insufficiency that cannot be diagnosed as Addison's disease. By virtue of this concept, adrenal fatigue dispels the notion that adrenal dysfunctions can only be defined by one of two extremes (*refer to figure 10)*. Indeed, the idea that pathology falls along a continuum that is not constrained by extreme cut-offs is becoming increasingly recognized in many fields of medicine, endocrinology included. That being said, despite prevailing symptoms (e.g., fatigue, cognitive deficit, hormonal imbalance, inability to cope with stress, insulin resistance, recurrent infection, reduced libido, sleep disturbance, suppressed immune system, weakness, etc.) current blood tests are often unable to detect small declines in adrenal function (Allen, 2013; Guilliams & Edwards, 2010). Moreover, there are a plethora of different hormonal combinations that can be present with measuring cortisol four times a day, rendering this condition difficult to ascertain via serum measures alone. Consequently, patients are often left untreated or misdiagnosed with alternative conditions including depression, chronic fatigue syndrome, or fibromyalgia.

Although the mechanisms of action of adrenal fatigue remains unknown, the predominant theory argues that symptoms of adrenal fatigue emerge when the adrenal glands are unable to keep up with the demands of chronic stress. As previously reviewed, when a stress is perceived the hypothalamus initiates a chain of commands that eventually results in the secretion of adrenal cortical hormones, most notably, cortisol (Tsigos & Chousos. 2002). In the short-term, the heightened release of cortisol is a highly adaptive response that prepares the body to deal with the perceived threat. Failure to shut down this response in times of chronic stress, however, can result in sustained cortisol release that leads to an array of maladaptive physiological responses, including hyperglycaemia, insulin resistance, and diabetes (Lee et al, 2013); immunosuppression (Dhabhar, 2009); hypertension, atherosclerosis, and cardiovascular disease (McEwan, 2004); increased risk for mental illness (McEwan, 2004); among much more. According to current theories, after a variable period of time (i.e., years) the adrenal glands are unable to keep up with the chronic secretion of cortisol imposed by chronic hyperactivation of the HPA axis (Guilliams & Edwards, 2010). Consequently, cortisol stores deplete inducing symptoms of hypocortisolism (i.e., adrenal fatigue).

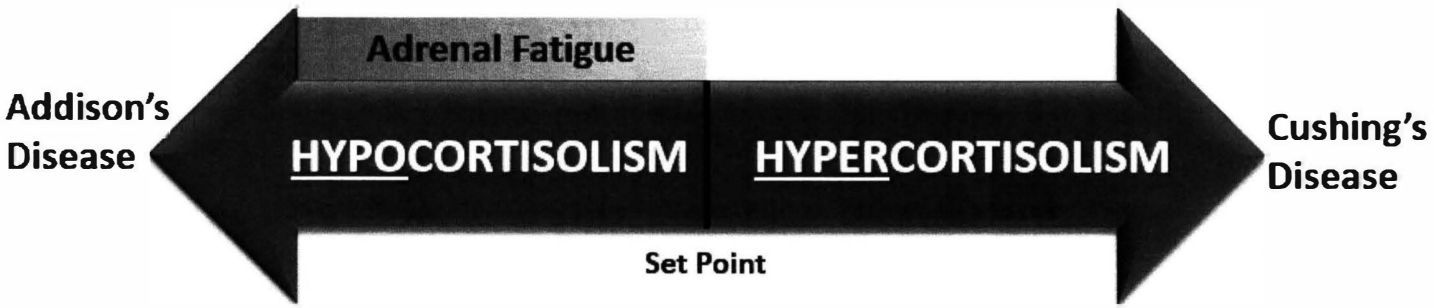


Figure 10. The spectrum of adrenal dysfunction

Treatment Protocol for Adrenal Fatigue

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Adrenal Fatigue	PO	Pregnenolone	10 mg – 60 mg q am	Utilizing pregnenolone and / or progesterone provides adrenal hormone precursors which allow the body to convert into needed hormone
	Topical	Pregnenolone	5 mg – 20 mg q am	Utilizing pregnenolone and / or progesterone provides adrenal hormone precursors which allow the body to convert into needed hormone
	PO	Progesterone	25 mg – 300 mg q hs	Utilizing pregnenolone and / or progesterone provides adrenal hormone precursors which allow the body to convert into needed hormone
	Topical	Progesterone	20 mg – 30 mg q am	Utilizing pregnenolone and / or progesterone provides adrenal hormone precursors which allow the body to convert into needed hormone
	PO	DHEA	Male 25 mg – 200 mg q am Female 5 mg – 25 mg q am	Protects immune system from excess cortisol secretion. Monitor for excess oestrogen conversion; oestradiol and oestriol
	Topical	DHEA	2 mg - 25 mg	Protects immune system from excess cortisol secretion.
	PO	Calcium Citrate 5- HTP	500 mg 50 mg	Can improve sleep
	PO	Hydrocortisone	Start with 5mg q am, could add BID depending on cortisol curve	Dosing is an attempt to mimic circadian rhythm. Take with food. Slowly wean off to prevent adrenal insufficiency.
	PO-SR	Hydrocortisone	15 mg – 30 mg q am	Dosing is an attempt to mimic circadian rhythm. Take with food. Slowly wean off to prevent adrenal insufficiency.
	PO	Phosphatidylserine	100 mg - 300 mg 1 to 2 times / day	Blocks endogenous cortisol release. Use for 1-3 months.
	PO	Melatonin	0.5 mg – 3 mg	High cortisol can suppress the production of melatonin; is a strong anti-oxidant.
	Sublingual Buccal	Melatonin	0.5 mg – 2 mg	High cortisol can suppress the production of melatonin; is a strong anti-oxidant.

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Inter-Hormone Relationships and Adrenal Function

Inter-Hormone Relationships and Adrenal Function: Special Consideration and Treatment Recommendations		
Hormone	**Resultant Effect**	**Treatment Recommendation**
Cortisol High & Melatonin Low	Cortisol suppresses melatonin, this contributes to sleep disruption	Give Melatonin to those patients with high night cortisol
DHEA Low & Testosterone Low	If both DHEA and testosterone are low, give DHEA	DHEA supplementation can raise test levels by 50% in females
Cortisol Low	If cortisol is low in AM, it may be low all day; it is usually the last to fall	Consider replacing cortisol with Cortef

SECTION VII: Adjunct Nutraceutical Therapy

Nutraceuticals

The term nutraceuticals was first coined in 1989 by Dr. Stephen DeFelice as a hybrid term of the words nutrition and pharmaceutical (Pandey et al., 2010). Reason being that nutraceuticals involve applying pharmaceutical technologies to nutritional sources in order to develop isolated concentrates of the nutrient's active ingredient. More specifically, **nutraceuticals** are defined as any bioactive substance that is isolated or purified from food sources to provide physiological and health benefits including the prevention and treatment of disease (Lockwood, 2010; Pandey et al., 2010). This includes dietary components (e.g., vitamins, minerals, essential fatty acids, and amino acids) as well as human metabolites extracted from plant or animal sources (e.g., coenzyme Q10, creatine, lipoic acid, etc.).

Nutraceuticals are typically consumed for one of the following reasons (Lockwood, 2010; Pandey et al., 2010):

- Re-establish endogenous nutrient levels that are in a deficient state
- Prevent or delay disease onset
- Manage or lessen symptom severity

Although there exists some variations from region-to-region, most countries recognize that nutraceuticals can be delivered in the form of functional foods or as dietary supplements. **Functional foods** are conventional foods that have been modified to exclude ingredients, add ingredients, or augment ingredients to promote health or prevent disease. Whereas **supplements** are pharmaceutically engineered oral dosages (e.g., tablets, capsule, powders, etc.) of a concentrated nutrient that can otherwise be found in foods. While functional foods hold a place in the nutraceutical market, dietary supplements make up the bulk of today's nutraceutical industry.

Quality Concerns

Despite the exponential growth rate of today's nutraceutical market, the quality and control of manufactured over-the-counter (OTCs) nutraceuticals continues to lag behind globally around the world (Mahabir & Pathak, 2010).

Dosage Strength

One of the major quality concerns with OTC supplements (that is current not regulated in most countries) is the variability in dosage strength seen from unit-to-unit. For example, highlighted in Lockwood's (2010) review article are published international evaluations of over 70 formulations of 25 different nutraceuticals, all of which display significant variability in compliance to the dosage strength indicated on the label. For example, in an Australian manufactured product of soy isoflavones, only 2 out of 10 units were found to be in compliance (i.e., ±5%) with the dosage strength indicated on the label (Howes and Howe, 2002). Moreover, the dosage strength varied from <1 to 100% of the label claim. We see even more alarming ranges in dosage strength with the evaluation of a US manufactured product of soy isoflavones, which ranged from 10-383% of the label claim (Setchel et al., 2001). These are just some example to name a few (*for more examples refer to the table on the subsequent page*).

Labelling

Of further concern, many OTC supplements recommend doses in their label instructions that, either vary greatly from one product to the next, or are well below the dose used in clinical trials. For example, the suggested daily doses of lutein have been reported to range from 0.25 to 22.5 mg, a factor difference of 90-folds (Lockwood, 2010). Moreover, most manufactured supplements are not required to follow manufacturing or compounding pharmaceutical standards of including a patient information leaflet or inset with their products. As such, patients are not counselled on the recommended dosage schedule, potential side effects, and possible interaction with other prescription medications. Furthermore, as the name implies, OTC supplements do not require a prescription. Consequently, patients largely self-treat without receiving expert advice.

Heavy Metals

Lastly, by virtue of being a naturally grown product, nutraceuticals are subjected to heavy metal contamination (Filipiak et al., 2015; Järup, 2003). Heavy metals are commonly defined as elements having a density of more than 5 g/cm^3. The adverse effects of heavy metals (e.g., cancer and neurotoxicity) are well documented and have been known for a long time, yet exposure to heavy metals continues and is even increasing in some parts of the world. Heavy metal contamination can occur naturally (i.e., weathering, biological activity, volcanic activity) or via anthropogenic sources (e.g., pesticides and chemical fertilizers, wastewater irrigation, precipitates from heavy coal combustion and smelter waste, as well as residues from mining). Unfortunately, unlike pharmaceuticals, nutraceutical bulk ingredients are not required to undergo heavy metal testing.

Compounding Solutions

As a compounding pharmacist, the quality of the final preparation is ultimately in their hands. High quality preparations can be attained by sourcing high-quality bulk ingredients (e.g., tested for heavy metals) and by implementing rigorous high-quality compounding preparatory techniques (e.g., proper trituration, geometric addition, compounding automation) and procedures (e.g., verifications and SOPs). Moreover, compounding requires a prescription; meaning that each preparation is tailored to the patient's specific needs based on professional practitioner recommendations. Taken together, in addition to the customization that can be achieved with compounding, compounders can also address current concerns with the quality of dietary supplements.

Proportion of Products in Compliance with Dosing Quality Standards for a Range of Nutraceutical Supplements

Nutraceutical	Origin	Proportion in Compliance (95-105%)	Range of Contents (% of label claim)
Carnitine[1]	Czech	1/3	50-104%
Carnitine[2]	USA	0/1	35%
β Carotene[3]	Germany	1/11	61-137%
β Carotene[4]	Canada	2/6	86-111%
Coenzyme Q10[5]	New Zealand	1/7	100-130%
Coenzyme Q10[6]	Japan	36/61	5-123%
Creatine[7]	USA	1/8	83-106%
Creatine[8]	USA	4/6	94-126%
DHEA[9]	USA	6/16	3 contain 0%, 1 contains 150%
DHEA[10]	USA	14/45	74-110%, 1 contained 0%
Docosahexaenoic acid[11]	USA	1/8	57-115%
Eicosapentanoic acid[11]	USA	0/8	75-94%
γ-Linolenic acid[12]	Australia	12/16	36-109%
Lipoic acid[13]	Austria	1/6	40-97%
Lutein[14]	USA	0/3	134-194%
Lutein[4]	Canada	0/2	109-125%
Lycopene[15]	Canada	1/6	6-143%
Melatonin[16]	Italy	5/6	93-102%
Oxyresveratrol[17]	USA	-	3/4 contained 0%
Resveratrol[18]	USA	2/4	94-97%
SAMe[19]	USA	4/12	40-120%
Soy isoflavones[20]	USA	4/32	10-383%
Soy isoflavones[21]	Australia	2/10	<1-100%
Soy isoflavones[22]	USA	2/13	47-99%
Green tea extracts[23]	USA	0/4	9-48%

Table adapted from: Lockwood, G.B. (2010). The quality of commercially available nutraceutical supplements and food sources. Journal of Pharmacy and Pharmacology, 63, 3-10.

References for the Table: Proportion of Products in Compliance with Dosing Quality Standards for a Range of Nutraceutical Supplements

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Nutraceutical Functions and Recommended Dosages

5-HTP (5 Hydroxytryptophan)

Functions

- Chemical precursor in the biosynthesis of serotonin
- Affects appetite, mood, and body temperature (Halford et al., 2005)
- May improve sleep quality (Hong, Park, & Suh, 2016)

Recommended Dosage

- 50 - 300 mg daily; Magnesium prolongs the effect of 5-HTP
- NOT recommended if patients are already on a selective-serotonin-reuptake inhibitor (SSRI)

Adrenal Cortical Extracts

Functions

- Adrenal cortical extracts obtained from porcine or bovine sources.
- Include adrenal cell contents, including nucleic acids, concentrated nutrients, and small amounts of adrenal hormones (Wilson, 2009)
- Supports, fortifies, and restores normal adrenal functions (Wilson, 2009)

Recommended Dosage

- 6-12 tablets per day (Wilson, 2009)
- 2-3 liquid vials under tongue per week (Wilson, 2009)

Alpha-Lipoic Acid

Functions

- Acts as a metal chelation (Rochette et al., 2013)
- Helps insulin work more effectively (Yang et al., 2014)
- Increases glutathione (Kleinkauf-Rocha et al., 2013)
- Slows brain aging (Farr et al., 2012)

Recommended Dosage

- 50 - 600 mg daily

Arginine

Functions

- Increases muscle blood volume (Alvares et al., 2012)
- Enhances fat metabolism and immune function (de Castro Barbosa et al., 2013; Ren et al., 2013)
- Important for gut health (Ishibashi-Shiraishi, 2016)
- Increases Human Growth Hormone production (Alba-Roth et al., 1988)
- Increases sperm count (Agarwal et al., 2014; Keller et al., 1975)

Recommended Dosage

- 1000 – 3000 mg daily

Side Effects and Toxicity

- Diarrhoea
- Increase in herpes simplex virus (HSV) outbreaks; Recommend giving lysine

Ashwaganda Root

Functions

- Anti-bacterial, anti-inflammatory, and antioxidant (Chandra et al., 2012; Devkar et al., 2014)
- Enhances endurance and strength (Sandhu et al., 2010)
- Helps preserve adrenal size (Kalani, Bahtiyar, & Sacerdote, 2012)
- Helps you deal with stress (Singh et al., 2016)
- Increases libido (Dongre, Langade, & Bhattacharyya, 2015)

Recommended Dosage

- 500 – 2000 mg daily

Side Effects

- Diarrhoea, nausea, and vomiting

Chromium

Functions

- Aids in fat loss and burns calories (Preuss et al., 2004)
- May decrease Total cholesterol and LDL; increases HDL (Burgos et al., 2016)
- Helps decrease sugar cravings (Hyman, 2013)
- Helps increase DHEA (Rubinstein & Federman, 2000)
- Helps regulate blood glucose levels (Suksomboon et al., 2014)

Recommended Dosages

- 50 - 200 mcg daily
- Higher doses for individuals with insulin resistance and high cholesterol up to 1000 mcg daily

Food Sources

- Brewer's yeast
- Ground beef
- Calf's liver
- Whole wheat bread
- Rye Bread

Coenzyme Q-10

Functions

- Enhances the regeneration of Vitamin E (Cane, 2001)
- Involved in energy-producing metabolic pathways (Alcázar-Fabra, Navas, & Brea-Calvo, 2016)
- Lowers blood pressure (Yang et al., 2015)
- Is an antioxidant (Lee, Huang, Chen, & Lin, 2012)

Recommended dosages

- 30 - 360mg daily

Side Effects and contraindications

- Diarrhoea/ heartburn/ nausea
- Palpitations
- Insomnia (dosages > 100mg)

Eleuthero (Siberian Ginseng)

Functions

- Acts as a stimulant (Li, 2001)
- Acts as an adaptogen (strengthens the body's resistance to stress) (Panossian, 2013;
- Act as an anti-inflammatory (Zaluski & Smolarz, 2016)
- Increases learning ability and mental awareness (Kim, 2013)

Recommended Dosage

- 500 – 1000 mg daily

Side Effects and Contraindications

- Can cause headaches or agitation
- Do NOT take if there is history of heart disease

Ferrous Glycinate

- Cofactor for conversion of T4 to T3

Indole 3 Carbinol

Functions

- Helps prevent the development of estrogen-enhanced cancers (Benninghoff & Williams, 2013)
- Antioxidant: Inhibits oxidation and the formation of free radicals (Li et al., 2013)

Recommended Dosage

- 300 - 500 mg

Iodine

- Involved in energy production and nerve function (Bourre, 2006)
- Maintains healthy breast tissue (Patrick, 2008)
- Needed for thyroid, breast, prostate, kidneys, spleen, liver, blood, salivary glands, and intestinal function (Cann, 2006; Patrick, 2008; Kleefeld, Zuchora, Fahy, & Moore, 2016; Zimmermann & Boelaert, 2015)

Licorice (Glycyrrhiza)

Functions

- Aids in reducing fevers, bronchial infections, chronic inflammation (e.g. arthritis), and autoimmune diseases (Hasan, Ali, Chishti, & Hussain, 2013)
- Treats adrenal dysfunctions (Savers, 2014)
- May help kill nitrosamines- carcinogens in food (Sakarkar & Deshmukh, 2011)

Recommended Dosage

- 200 mg

Side Effects

- May not be able to take with HTN, liver, or kidney disease

Magnesium (Long & Romani, 2014)

- Involved with processes related to over 300 enzymes
- Acts as an anticonvulsant
- Necessary for protein synthesis
- Removes excess ammonia
- Methylsulphonylmethane (MSM)
- Supplies sulphur to your body
- Treats pain and inflammation
- Magnesium glycinate has greatest bioavailability

Melatonin

Functions

- Acts as an antioxidant (Bonnefont-Rousselot, 2014; Ding et al., 2014)
- Decreases atherosclerosis (Favero et al., 2014)
- Helps get you to sleep and stay asleep (Hardeland et al., 2006)
- Strengthens the immune system (Carrillo-Vico et al., 2013; Szczepanik, 2007)

Recommended Dosages

- 1 - 6 mg daily

Milk Thistle

Functions

- Decreases blood sugar (Kazazis et al., 2014)
- Increases HDL, and lowers LDL (Coon & Ernst, 2003)
- Protects your liver from damage due to toxins (Abenavoli et al., 2010)

Recommended Dosage

- For Diabetes: 250 mg split BID
- For liver disease: 400 mg split BID
- To increase glutathione levels: 150 - 300 mg split BID

Omega 3 Fatty acids (ALA, DHA, EPA)

Functions

- Crucial for many brain functions (Witte et al., 2013)
- Decrease inflammation (Calder, 2015)
- Lowers cholesterol (Savinova et al., 2015)
- Enhance insulin function (Talukdar et al., 2010)
- May decrease homocysteine levels (Martinez-Vega et al., 2015)

Phosphatidyl Serine

Functions

- Critical for Neurotransmission (Glade & Smith, 2015)
- Reduces Cortisol (Hellhammer et al., 2012)
- Immune function (Birge et al., 2016)

Recommended Dosage

- 100 - 500 mg daily

Rhodiola

Functions

- Increases Immunity (Skopir'liska-Roiewska, 2008)
- Decreases inflammation (Shanely et al., 2014)
- Affects the levels of neurotransmitters – can help treat stress (Spasov et al., 2000)

Recommended Dosage

- 50 mg BID

Saw Palmetto

Functions

- Anti-androgenic effects (Kodama et al., 2013)
- May be effective in treating male pattern baldness (Kodama et al., 2013)

Recommended Dosage

- For Women: 250 mg BID
- For Men: 160 mg BID

Selenium

- Deiodinases the thyroid (Drutel, Archambeaud, & Caron, 2013)
- Needed for immune system (Yuan et al., 2015)
- Works with vitamin E as an antioxidant (Yuan et al., 2015)
- Reduces heavy metal toxicity (Siscar, Koenig, Torreblanca, & Sole. 2014)

Theanine

Functions

- Decreases anxiety, helps promote relaxation (Liang et al., 2015)
- Supports brain health by improving focus and attention (Liang et al., 2015)
- Increases serotonin levels (Liang et al., 2015)

Recommended Dosages

- 100 – 400 mg daily

Vanadium

Functions

- Aids in metabolism of glucose; Synergistic effect when given with Chromium (Fedorova et al., 2013)
- Improves insulin sensitivity (Domingo & Gomez, 2016)

Recommended Dosages

- 10- 50 mg daily; Do not take more!

Symptoms of Toxicity

- Increased blood pressure
- Increased triglycerides

Vitamin B-5 (Pantothenic acid) (Sechi et al., 2016; Zempleni et al., 2013)

- Co-factor for Coenzyme A
- Aids in formation of antibodies
- Aids in wound healing
- Helps with fatty acid transport
- Needed to make fatty acids
- Stimulates adrenal gland
- Helps your body use other vitamins
- Helps convert food into energy
- Used in synthesis of several amino acids

Vitamin B-6 (Pyridoxine) (Stover & Field, 2015; Zempleni et al., 2013)

- Detoxifies chemicals
- Aids in neurotransmitter synthesis (tryptophan to serotonin)
- Needed for REM sleep
- Absorption of fats and proteins
- Helps with immune system
- Production of HCL
- Transfer of amino acid groups
- Used in methylation process; lowering homocysteine levels

Vitamin B-7 (Biotin) (Zempleni et al., 2013)

- Adds a carboxyl group to substrates
- Plays a role in carbon dioxide fixation
- Fatty acid biosynthesis
- Replenishment of citric acid cycle
- Increases insulin sensitivity
- Strengthens nails
- Used in energy metabolism

Vitamin B-9 (Folate) (Bottiglieri, 2013; Zempleni et al., 2013)

- Detoxifies hormones
- Essential for DNA synthesis
- Involved in methylation
- Metabolic conversion of dopamine
- Needed for synthesis of haemoglobin
- Produces SAMe

Vitamin B-12 (Cobalamin) (Bottiglieri, 2013; Zempleni et al., 2013)

- Essential for DNA synthesis
- Facilitates the metabolism of folic acid
- Functions as a methyl donor
- Involved in production of neurotransmitter
- Required for nervous system function and proper digestion

Vitamin C (Rodrigo, Prieto, & Castillo, 2013)

- Involved in collagen formation and neurotransmitter formation
- Increases WBCs and interferon (immune system)
- Decreases adrenal steroid production
- Helps carnitine synthesis
- Breaks down fatty acids and releases energy
- Helps metabolise tyrosine
- Involved in catecholamine synthesis and production of serotonin
- Needed for progesterone production

Vitamin D (Bikle, 2014)

- Steroid hormone
- Assists with calcium homeostasis and absorption in gut
- Assists with conversion of T4-to-T3
- Helps pancreas release insulin
- Necessary for blood clotting

Vitamin E (Niki, 2014)

- Antioxidant for fatty acids
- Improves the action of insulin
- Increases your immune system
- Inhibits platelet adhesion
- Needed for proper ovary function

Zinc (Yi, Huang, & Zhou, 2015)

- Multiple enzyme processes: DNA replication, protein synthesis, and cell division
- Vital to immune system and thyroid functioning
- Essential component of hormones
- Enhances biochemical actions of Vitamin D
- Inhibits DHT
- Helps balance blood sugar levels
- Metabolises carbohydrates

SECTION VIII: Special Considerations Related to Treatment Protocols

Life Cycle-Related Considerations

Considerations Related to Early Onset of Menarche:

It has been estimated that the average age of menarche (beginning of menses) is shy of 12-years-old and has been declining slowly over decades. When menarche begins, it is a physical indicator that endogenous oestrogen levels are sufficient to cause endometrial growth.

The clinical significance of this is as follows:

- Higher levels of oestrogen exposure have begun and will continue interrupted until menopause
- Ovulation has, or will soon begin
- Corpus luteum will begin to produce progesterone

Early onset of menarche is characterised by higher levels of circulating oestradiol, which can result in the presentation of symptoms and disorders related to oestrogen dominance, oestrogen related imbalances, and resulting pathologies. For example, early onset menarche is consistently associated with increased risk of premenopausal and postmenopausal breast cancer (Colditz et al., 2014). Indeed, in a meta-analysis of 100 epidemiological studies, it was found that for every one-year decrease in age at menarche the risk of developing breast cancer increases by 5% (Collaborative Group on Hormonal Factors in Breast C., 2012).

Early onset of menarche begins the process of viable follicle and egg loss relatively early resulting in a decreased ability to form a dominant follicle with a viable egg. These 'older' follicles are sometimes unable to form a viable corpus luteum resulting in inadequate amounts of progesterone production.

Group Discussion / Interactive Learning:

- Instruction: What are the consequences and potential risks associated with the above facts related to time onset of menarche?

Considerations for Menstrual Cycle Length:

Women whose cycles are shorter than 25 days have a 200% increased risk of breast cancer. The more menstrual cycles, the more oestradiol produced, and the greater the oestrogen exposure and risk. If a patient presents with an average cycle length 25 days or less, then breast cancer risk doubles. Consideration should be given to luteal phase progesterone supplementation. Consequences of long-term oestrogen exposure will need to be considered during clinical surveillance. A careful consideration of the risk-benefit for oestrogen restoration must be made.

Consideration of Onset of Menopause:

Early menopause causes a woman's hormone levels to decrease sooner than normal. Indeed, early menopause reduces the number of cycles and thus the risk of oestrogen related pathologies. Since oestrogen can encourage the growth of some types of breast cancer this decrease of oestrogen can help lower the risk of developing breast cancer. Conversely, early menopause reduces the number of times ovulation takes place which decreases the risk for other oestrogen related cancers such as ovarian and uterine. If a woman has had a late onset of menopause, then oestrogen related cancer risk may be increased. Consideration should be given for progesterone supplementation. Consequences of long-term oestrogen exposure will need to be considered in clinical surveillance. Careful consideration of the risk-benefit for oestrogen restoration must be made.

Non-Ovulating Premenopausal Circumstance Considerations

Ovulation is necessary in order to produce the corpus luteum and is responsible for progesterone production during the later stage of the menstrual cycle.

Group Discussion / Interactive Learning:

- Instruction: What are the consequences and potential risks associated with a non-ovulating premenopausal circumstance that lasts for a prolonged period of time? What treatment protocols might be beneficial?

Pregnancy and Lactation-Related Considerations

Considerations in Pregnancy History:

Pregnancy lowers oestrogen exposure and since oestrogen fuels many of the oestrogen related pathologies a woman's risk is decreased each time she is pregnant. Pregnancy before age 30 reduces a woman's total number of lifetime menstrual cycles, which is thought to be one reason they help lower your risk. According to the National Cancer Institute, having a full-term pregnancy at or before age 20 offers the most protection against developing breast cancer cutting the risk in half. (Bernstein, 2002) If the patient has had one or less pregnancies, then total oestrogen exposure is increased. If a woman becomes pregnant at 30 years old or greater, then her risk of breast cancer is increased (Bernstein, 2002). Consequences of excess oestrogen stimulation will need to be considered in clinical surveillance.

Time Frame from Menarche to First Full-Term Pregnancy:

The shorter the time frame between onset of menses and first full-term pregnancy, the lower the risk of breast cancer (Colditz et al., 2014; Li et al., 2008). Reason being, that breast tissue undergoes significant proliferation from the first menses till the first full-term pregnancy, at which point breast cells mature and are less affected by menstrual cycle hormones and are thus more resistant to breast cancer.

If a woman has early onset menses and/or bores her first child late in reproductive life, then she has a higher likelihood of oestrogen related pathologies and consideration should be given to progesterone supplementation. Consider clinical monitoring related to excess oestrogen stimulation and the risk-to-benefit ratio related to oestrogen restoration.

Considerations Related to Duration of Lactation:

Women that breastfeed have statistically reduced risk of developing breast cancer (Kumar et al., 2014. It has been shown that breast cells mature during lactation and are less affected by menstrual cycle hormones and more resistant to breast cancer. Studies have indicated that the longer a woman breast feeds, the longer ovulation is suppressed, thus the lower the risk for premenopausal breast cancer. In one report, it was found that breast cancer risk decreased by 7% for every 12 months of breastfeeding (Huo et al., 2008).

If a woman does not nurse her newborn or the duration of nursing and its associated lactation is less than three months, then she may have a higher incidence of breast cancer. Consider progesterone supplementation. Consider clinical monitoring related to excess oestrogen stimulation and the risk-to-benefit ratio related to oestrogen restoration.

Cancer Risk-Related Considerations

Considerations related to Prior Use of Synthetic Oestrogen:

Oestrogen is implicated in many instances of breast, ovarian and endometrial cancer risk. Oestrogen-related contributing factors include (Hilakivi-Clarke et al., 2013):

- Its role in stimulating breast cell division
- Its work during the critical periods of breast growth and development
- Its effect on other hormones that stimulate breast cell division
- Its support of the growth of oestrogen-responsive tumours

If a woman has used conventional oestrogens or synthetic hormone therapy for more than five years, then the risk of oestrogen related cancer is nearly doubled. Progesterone with I3C or DIM, and Vitamin D3 supplementation to decrease breast, ovarian and endometrial hyperplasia and promote cellular apoptosis should be considered. Consequences of long-term oestrogen exposure will need to be considered in clinical surveillance.

Considerations Related to Use of Oral Contraceptives:

It has been reported those women who:

- Used oral contraceptives before the age of 25 and had breast cancer susceptibility gene 1 (*BRAC1*) had increased risk for early-onset breast cancer. This risk increases with duration of use (Kostopoulos et al., 2014)
- Used oral contraceptives for ≥ 5 years between ages 20 and 39 increased the risk for oestrogen-related breast cancer (Beaber et al., 2014)

In contrast, some studies suggest that the longer a woman takes oral contraceptives, the lower her chance of developing ovarian cancer. Many studies demonstrated a 40% - 50% reduction of risk for ovarian cancer. These studies also found that the use of oral contraceptives may protect against endometrial cancer (Gierisch et al., 2013).

Lifestyle-Related Considerations

Considerations Related to Diet and Exercise:

- A high fat diet can result in an earlier onset of menarche which can result in an increased life-time exposure to oestrogen (Zhuo et al., 2014).
- High unsaturated fat diets are linked to breast cancer, in both the quantity and quality of fat (Sieri et al., 2014).
- Hydrogenated fats, found in margarine, form trans-fatty acids which are carcinogenic (Laake et al., 2013.
- Linoleic acid, found in nuts, corn oil, and most margarine, upregulates growth of breast cancers (Mouradian et al., 2014).
- Higher red meat intake is associated with elevated risk of breast cancers (Cho et al., 2006).
- Approximately 25% of cancer cases, globally, are due to excess weight and sedentary lifestyle (McTiernan, 2008).
- Alcohol consumption increases the risk of developing cancers of the oral cavity, pharynx, oesophagus, colon, liver, larynx, and female breast (Bagnardi et al., 2015).

Considerations Related to Body Type:

Body size can represent and suggest many things about an individual's health status and risk. Obesity is associated with pre-menstrual syndrome. In post-menopausal women not taking exogenous hormones, general obesity is a significant predictor of breast cancer. More fat cells produce more oestrogen. Fat cells can be a source of the enzyme aromatase that converts the body's androgens into oestrogens thus increasing the body's oestrogen burden.

- The increased risk for breast cancer that is associated with larger BMIs is due to the greater bioavailability of circulating oestradiol (Endogenous Hormones Breast Cancer Collaborative Group, 2003)
- Abdominal obesity is associated with an elevated risk of breast cancer; Women with high waist-to-hip ratios have a 1.62-fold increase in developing breast cancer (Connolly et al., 2002)

SECTION IX: PMS, Perimenopause, and Menopause

Treatment Protocol for Premenstrual Syndrome

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Premenstrual Syndrome	Oral	Progesterone	25 mg - 400 mg [50 - 200 mg]	Administration: 1 treatment / day Administration: Luteal phase (Cycle days 15-28) Can start before ovulation if symptomatic (Cycle day 10)
	Topical	Progesterone	5 mg - 50 mg [10 -20 mg]	Administration: Luteal phase (Cycle days 15-28) Administration: 1 - 2 applications / day

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Treatment Protocol for Perimenopause

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Perimenopause	Oral	Progesterone [Micronized SR]$^{\Psi}$	25 mg – 400 mg [50 – 200 mg]	Administration: Luteal phase (Cycle days 8-28) If no predictable cycle: Continue dosing until next menses.
	Topical	Progesterone	5 mg – 50 mg [15 – 25 mg]	Administration: Luteal phase (Cycle days 8-28) If no predictable cycle: Continue dosing until next menses. Administration: 1 application / day
	Topical	Oestriol : Oestradiol Ratio [50 : 50]	0.05 mg – 0.25 mg	Administration: 1 applications / day If patient cycling; then no oestrogen If low oestrogen range test; then start biest **Do not administer without Progesterone**

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Treatment Protocol for Surgical Menopause

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Surgical Menopause	Oral	Progesterone [Micronized SR]	25 mg - 400 mg [100 mg - 200 mg]	Administration: 1 treatment / day Discontinue 4 days / month or 1 day / week
	Topical	Progesterone	10 mg - 50 mg [20 mg - 25 mg]	Administration: 1-2 applications / day Discontinue 4 days / month
	Topical	Oestradiol : Oestriol Ratio [50 : 50]	0.10 mg - 0.50 mg starting dose	Administration: 1-2 applications / day Younger patients may need higher doses Discontinue 1 day / week
	Topical	Testosterone	0.25 mg - 2.00 mg [0.50 mg]	Administration: 1 application / day Consider replacing testosterone with DHEA if patient positive for adrenal dysfunction
	Oral	DHEA	5.00 mg – 20.00 mg [5 mg - 10 mg]	Administration: 1 treatment / day in morning
	Topical	DHEA	0.50 mg - 2.50 mg	Administration: 1 treatment / day in morning

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Treatment Protocol for Natural Menopause

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Natural Menopause	Oral	Progesterone [Micronized SR]	25 mg - 400 mg [100 mg - 200 mg]	Administration: 1 treatment / day Discontinue 4 days / month or 1 day / week
	Topical	Progesterone	10 mg - 50 mg [20 mg - 25 mg]	Administration: 1-2 applications / day Discontinue 4 days / month Quantity sufficient to suppress endometrial lining
	Topical	Oestradiol : Oestriol Ratio [50 : 50]	0.10 mg - 0.50 mg starting dose	Measure: Treatment may not be necessary Administration: 1-2 applications / day Discontinue 1 day / week
	Topical	Testosterone	0.25 mg - 2.00 mg [0.50 mg]	Measure levels as treatment may not be necessary. Consider replacing testosterone with DHEA if patient positive for adrenal dysfunction.
	Oral	DHEA	5.00 mg – 20.00 mg [5 mg - 10 mg]	Administration: 1 treatment / day in morning
	Topical	DHEA	0.50 mg - 2.50 mg	Administration: 1 treatment / day in morning

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Inter-Hormone Relationships and Ovarian Function

Inter-Hormone Relationships and Ovarian Function: Special Considerations and Treatment Recommendations

Hormone	Resultant Effect	Treatment Parameter
FSH High & Inhibin B Low	FSH is only a measurement of ovarian reserve	High FSH does not necessarily mean low E2 levels in perimenopause
Oestradiol High & TBG or SHBG High	Oestrogen increases binding proteins	Thyroid hormone and testosterone will be more bound and less free hormone. Consider functional hypothyroidism. Thyroid test could be normal, as well as low testosterone
Progesterone Normal & Oestradiol High	Progesterone antagonizes oestrogen by down regulating its receptor	Can bring oestrogen into range; Consider giving progesterone even if level normal in the presence of high E2
Testosterone High & DHT High	At high levels of Testosterone, 5-alpha reductase favours conversion to DHT	Consider blocking 5-α reductase for side effects of hirsutism and acne with high testosterone
Progesterone Normal & DHT Normal or High	Progesterone blocks 5 alpha reductase	Giving progesterone should help acne
Progesterone Low		Replace progesterone
Testosterone High & Oestradiol Low	Think about excess Test aromatizing to Oestrone, contributing to Oestrogen Dominance	Consider checking androstenedione or E1. Patient may not actually be low in E2

CASE STUDY 1

Case Description:

Jennifer, a working mom presents for consultation with heavy periods every 26 days that last 8 days. Her chief complaints include night sweats, difficulty sleeping, breast tenderness, and bloating. She remarks that she has not been as efficient with her multitasking as she used to be. The worse symptom is her terrible PMS. Not only does she take it out on her husband and children, but she has also lost her temper with clients, causing her to lose out on a few high profile clients. She saw her gynaecologist who ordered a battery of tests. He told her she was not in menopause and prescribed an antidepressant. She has been taking them for four months now and has put on 15 pounds (7 kg). She presents for consultation for hormone restoration.

Instructions:

1. Work in your small groups.
2. Review all the details provided to you in the case.
3. Use any and all seminar-related tools and charts to help establish a treatment plan.
4. Apply the fundamental principles of hormone therapy and rules of engagement.
5. Determine the tests to be performed and what may be incorrect with current treatment plan.
6. Discuss a *traditional* pharmacotherapeutic plan based on customary practices and standards
7. Discuss a *personalised non-traditional* pharmacotherapeutic plan by taking into account a more appropriate dose, dosage form, route of delivery, and delivery system.
8. Discuss possible *complimentary* therapies.
9. Discuss the risks and benefits or your therapeutic plans.
10. Prepare to provide a verbal summation of the following:
    - Hormone-related abnormalities
    - Rules of engagement followed and fundamental principles respected
    - Traditional pharmacotherapeutic plan
    - Non-traditional pharmacotherapeutic plan: Drug agent selection, route of delivery, and delivery system.
    - Complimentary therapy
    - Risk ← → Benefit assessment for traditional and non-traditional pharmacotherapeutic plans

Case Study 1: Patient Evaluation Form

PATIENT INFORMATION									
Name:	Jennifer					Age:	45	Sex:	F
Height:	5' 4"	Weight:	140 lbs	HR:	90	Systolic:	138	Diastolic:	84

PRIOR MEDICAL HISTORY								
○	Allergies	○	Osteopenia	○	Amenorrhea	○	Menarche:	11
○	Cancer: Breast	○	Osteoarthritis	○	Oligomenorrhea	○	Pregnancies:	2
○	Cancer: Ovarian	○	Arteriosclerosis	○	Dysmenorrhea	○	Lactation:	None
○	Cancer: Uterine	○	Heart Disease	●	Endometriosis	○	Miscarriages:	None
○	Cancer: Prostate	●	High Cholesterol	○	Hysterectomy	○	Infertility:	N
○	Clinical Depression	○	Hypertension	○	Oophorectomy	○	Body Fat:	40 %
○	Diabetes Type 1	○	Hypotension	○	Hyperthyroid	○	Waist:	36"
○	Diabetes Type 2	○	Hypoglycaemia	○	Hypothyroid	○		
○	Osteoporosis	○	Stroke	○	Yeast Infection	○		

PAST AND CURRENT MEDICATION HISTORY							
○	Oral Contraceptives	○		○	Hormone Therapy	○	
○		○		○		○	
○		○		○		○	
○		○		○		○	

LIFESTYLE ASSESSMENT									
○	Caffeine Consumption	○	Metallurgical Toxicities	●	Cardiovascular Exercise		○	Dietary Habits
○	Alcohol Consumption	○	Chemical Exposures		Frequency:	2 x / week	○	Vegetarian
○	Tobacco Utilization	○	Chemical Sensitivities		Intensity:	Moderate	○	Carbohydrates
○	Recreational Drugs	○	Shift Work		Duration:	1 hour	○	Proteins
○		○	Psychological Stress	○	Weight Training		○	Fats: Saturated
○		○	Time Zone Travel		Frequency:		○	Fats: Unsaturated
○		○	Current Season		Intensity:		○	
○		○			Duration:		○	

FAMILIAL MEDICAL HISTORY						
○	Allergies	○	Osteopenia	○	Amenorrhea	○
○	Cancer: Breast	○	Osteoarthritis	○	Oligomenorrhea	○
○	Cancer: Ovarian	○	Arteriosclerosis	○	Dysmenorrhea	○
●	Cancer: Uterine	○	Heart Disease	○	Endometriosis	○
○	Cancer: Prostate	○	High Cholesterol	○	Hysterectomy	○
○	Clinical Depression	○	Hypertension	○	Oophorectomy	○
○	Diabetes Type 1	○	Hypotension	○	Hyperthyroid	○
●	Diabetes Type 2	○	Hypoglycaemia	○	Hypothyroid	○
○	Osteoporosis	○	Stroke	○	Premature Menopause	○

Case Study 1: Patient Signs and Symptoms Chart

Subjective Symptoms: Alphabetical	Rating	InE	DeE	InP	DeP	InT	DeT	InD	DeD	InC	DeC	InI	DeTh
Acne	2		2	2	2	2		2					
Anxiety / Nervousness	5	5		5	5			5		5			
Apathy		0					0		0		0		
Breast Tenderness	5	5		5	5								5
Brittle Nails													0
Burned Out Feeling		0					0		0		0		0
Chemical Sensitivities									0		0		
Cold Body Temperature					0						0		0
Cold Extremities			0				0				0		0
Confusion			0		0					0			0
Constipation	2			2								2	2
Cramping Abdominal			0		0								0
Cravings for Sweet	3				3						3	3	
Decreased Concentration	3		3		3	3			3	3			3
Decreased Sex Drive	3	3	3		3		3		3	3			3
Decreased Sexual Sensation		0	0		0		0		0				0
Decreased Stamina							0		0		0		0
Deepening of Voice			0			0		0					0
Depressed Mood	2	2	2		2		2		2	2			2
Dry Eyes			0				0						0
Dry Skin / Hair			0				0		0				0
Fatigue	3		3				3		3		3		3
Fibrocystic Breasts	5	5			5								5
Fluid Retention Abdomen	4	4		4	4					4			
Fluid Retention Extremities	2	2			2					2			2
Foggy Thinking	4		4	4			4			4			4
Headaches	4	4	4	4	4		4						4
Heart Palpitations	2	2	2		2					2			2
Heavy & Irregular Menses	5	5		5	5								5
Hoarseness					0								0
Hot Flashes	4		4		4					4		4	4
Hypoglycemia										0	0	0	
Increased Facial and / or Body Hair			0		0	0	0					0	
Increased Hair Loss			0			0		0					0
Irritability	4	4			4	4		4		4			
Joint Pains			0				0		0		0		0
Low Blood Pressure											0		
Memory Problems	3		3				3		3	3			
Mood Swings	5	5	5	5	5	5				5			
Muscle Pain							0		0		0		0
Night Sweats	4		4		4					4			4
Numbness Hands and Feet												0	
Painful Intercourse	2		2		2		2						
Premenstrual Syndrome		0			0								
Salt Craving									0		0		
Sleep Disturbances	4		4	4	4					4			4
Swollen Eyes													0
Tearfulness		0	0		0								
Thinning Skin			0				0		0	0			0
Tired But Wired							0		0	0			0
Urinary Incontinence			0		0		0						
Vaginal Dryness			0		0		0						
Weight Gain: Hips		0		0	0								0
Weight Gain: Waist		0		0	0	0		0		0		0	0
Number of symptoms ≥ 3	17	9	10	8	14	3	5	2	4	11	2	2	11
Number of *hormone* symptoms ≥ 3 / Number of *rated* symptoms ≥ 3	-	9/17	10/17	8/17	14/17	3/17	5/17	2/17	4/17	11/17	2/17	2/17	11/17
% Expression	-	53	59	47	82	18	29	12	23	65	12	12	65

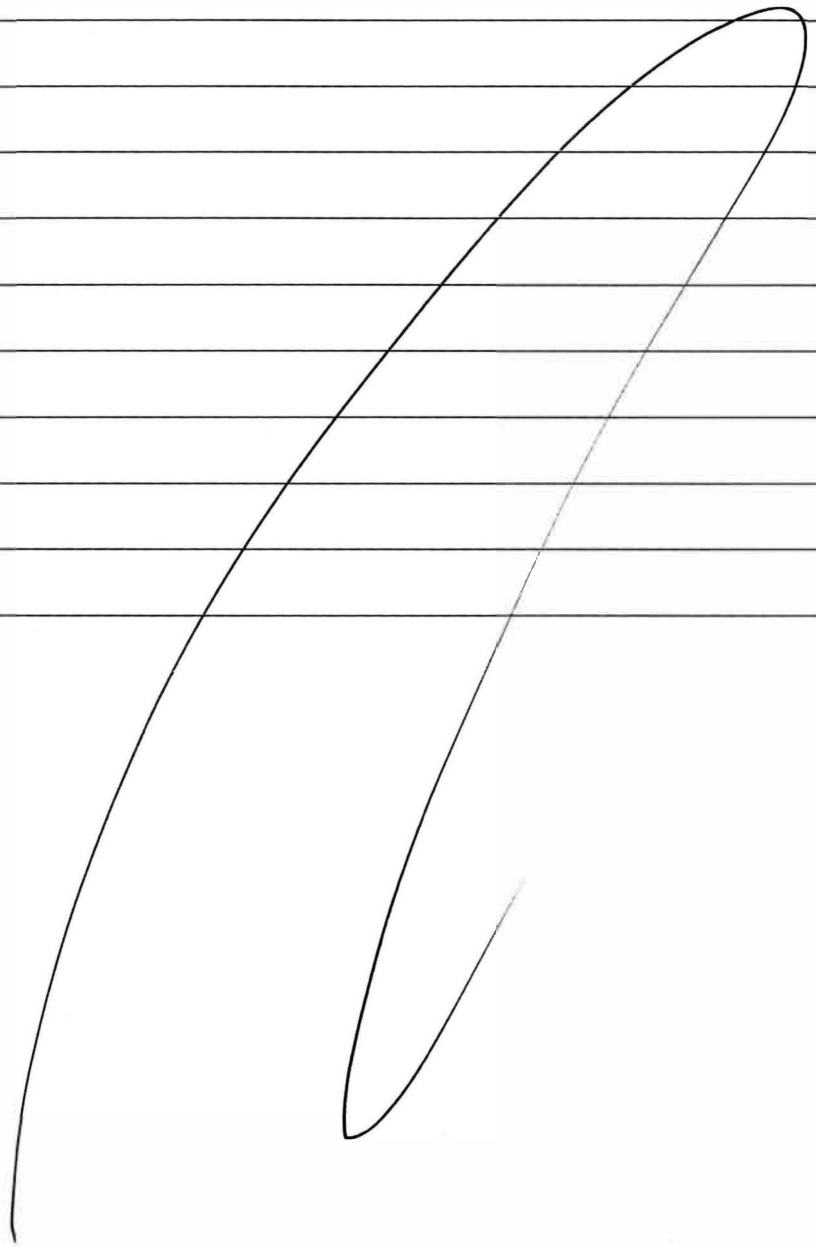
DE = Decreased; In = Increased; E = Oestrogen; P = Progesterone; T = Testosterone; D = DHEA; C = Cortisol; I = Insulin; Th = Thyroid

Case Study 1: Test Selection Form

	TEST RESULTS					
	TEST TYPE	SOURCE	RESULT	L – N – H	RANGE	UNITS
o	**17-OH Progesterone**					
o	*Males*	Blood			1.8 – 10.4	nmol/L
o	*Females (Follicular phase)*	Blood			<3.3	nmol/L
o	*Females (Luteal phase)*	Blood			2.9 – 15.1	nmol/L
o	**25-OH Vitamin D**	Blood			50 – 150	nmol/L
o	**Androstenedione**					
o	*Female* (>18 yrs)	Blood			1 – 11.5	nmol/L
o	*Male* (>18 yrs)	Blood			2.1 – 10.8	nmol/L
o	**Cortisol**					
o	*Random*	Blood			70 - 550	nmol/L
o	*Morning*	Blood			110 - 550	nmol/L
o	*Evening*	Blood			70 – 400	nmol/L
o	*Morning*	Saliva			3.9 – 13.5	umol/L
o	*Midday*	Saliva			1.2 – 4.8	umol/L
o	*Evening*	Saliva			0.5 – 3.7	umol/L
o	*Night*	Saliva			0.3 – 2	umol/L
o	**DHEA**	Saliva			0.3 – 1.8	nmol/L
o	**DHEAS**					
o	*Female (15 – 20 yrs)*	Blood			5.2 – 7.5	umol/L
o	*Female (21 – 24 yrs)*	Blood			2.5 – 9.6	umol/L
o	*Female (25 – 34 yrs)*	Blood			1.4 – 8.7	umol/L
o	*Female (35 – 44 yrs)*	Blood			1.8 – 7.8	umol/L
o	*Female (45 – 55 yrs)*	Blood			0.7 – 5.4	umol/L
o	*Female (>56 yrs)*	Blood			0.8 – 3.2	umol/L
o	*Male (15 – 20 yrs)*	Blood			5.3 – 8.5	umol/L
o	*Male (21 – 24 yrs)*	Blood			3.7 – 10.2	umol/L
o	*Male (25 – 34 yrs)*	Blood			4.8 – 13.9	umol/L
o	*Male (35 – 44 yrs)*	Blood			2.2 – 12.4	umol/L
o	*Male (45 – 55 yrs)*	Blood			1.9 – 11.5	umol/L
o	*Male (>56 yrs)*	Blood			0.9 – 5.9	umol/L
o	**Dihydrotestosterone** (*Male*)	Blood			0.4 – 2.5	nmol/L
o	**Oestradiol (E2)**					
o	*Male*	Blood			<150	pmol/L
o	*Female (Follicular phase)*	Blood			70 – 130	pmol/L
o	*Female (Midcycle peak)*	Blood			230 – 1300	pmol/L
o	*Female (Luteal phase)*	Blood			200 – 790	pmol/L
o	*Female (Postmenopausal)*	Blood			<121	pmol/L
o	*Male*	Saliva			<8	pmol/L
o	*Female (Follicular phase)*	Saliva			2 – 8	pmol/L
o	*Female (Luteal phase)*	Saliva			6 – 17	pmol/L
o	*Female (Postmenopausal)*	Saliva			2 – 7	pmol/L
o	**Oestriol (E3)**					
o	*Male*	Saliva			3.5 – 20	pmol/L
o	*Female (Follicular phase)*	Saliva			3.5 – 98	pmol/L
o	*Female (Luteal phase)*	Saliva			3.5 – 98	pmol/L
o	*Female (Postmenopausal)*	Saliva			3.5 – 24	pmol/L
o	**Oestrone (E1)**					
o	*Male*	Saliva			39 – 58	pmol/L
o	*Female (Follicular phase)*	Saliva			43 – 64	pmol/L
o	*Female (Luteal phase)*	Saliva			39 – 58	pmol/L
o	*Female (Postmenopausal)*	Saliva			39 – 58	pmol/L
o	**FAI** (free androgen index)					
o	*Female (Premenopausal)*	Blood			0.3 – 9.8	
o	*Female (Postmenopausal)*	Blood			0.2 – 6.0	
o	**Ferritin**					
o	*Male (<15 years)*	Blood			20 – 250	ug/L
o	*Female (15 – 50 yrs)*	Blood			10 – 120	ug/L
o	*Female (>50 yrs)*	Blood			15 – 220	ug/L

o	**FSH**					
o	*Male*	Blood			1 – 8	IU/L
o	*Female (Follicular phase)*	Blood			4 – 16	IU/L
o	*Female (Midcycle peak)*	Blood			8 – 30	IU/L
o	*Female (Luteal phase)*	Blood			2 – 12	IU/L
o	*Female (Post-menopausal)*	Blood			>24	IU/L
o	**FT3**					
o	13 – 21 yrs	Blood			4.7 – 7.2	pmol/L
o	>21 yrs	Blood			3.5 – 6.5	pmol/L
o	**FT4**	Blood			9 – 25	pmol/L
o	**LH**					
o	*Male*	Blood			2 – 8	IU/L
o	*Female (Follicular phase)*	Blood			<16	IU/L
o	*Female (Midcycle phase)*	Blood			15 – 75	IU/L
o	*Female (Luteal phase)*	Blood			<16	IU/L
o	*Female (Postmenopausal)*	Blood			>24	IU/L
o	**Progesterone**					
o	*Male*	Blood			<5	nmol/L
o	*Female (Follicular phase)*	Blood			<6	nmol/L
o	*Female (Midcycle peak)*	Blood			>29	nmol/L
o	*Female (Luteal phase)*	Blood			10 – 70	nmol/L
o	*Female (Postmenopausal)*	Blood			<2	nmol/L
o	*Female (Follicular phase)*	Saliva			<5.0	nmol/L
o	*Female (Luteal phase)*	Saliva			10 – 70	nmol/L
o	*Female (Postmenopausal)*	Saliva			<1.0	nmol/L
o	**Prolactin**					
o	*Male*	Blood			45 – 375	mIU/L
o	*Female (Premenopausal)*	Blood			60 – 620	mIU/L
o	*Female (Postmenopausal)*	Blood			40 – 430	mIU/L
o	**PSA**					
o	<50 yrs	Blood			<2.6	ug/L
o	50 – 60 yrs	Blood			<3.6	ug/L
o	60 – 70 yrs	Blood			<4.6	ug/L
o	>70 yrs	Blood			<6.6	ug/L
o	**Quantitative HCG**					
o	*Male*	Blood			<5	IU/L
o	*Female* (pregnant)	Blood			>25	IU/L
o	**Reverse T3**	Blood			140 - 540	pmol/L
o	**SHBG**					
o	*Male*	Blood			15 – 50	nmol/L
o	*Female*	Blood			15 – 100	nmol/L
o	**Testosterone, Free**					
o	*Male*	Blood			200 – 600	pmol/L
o	*Female*	Blood			8 – 55	pmol/L
o	*Male*	Saliva			207 – 1173	pmol/L
o	*Female*	Saliva			25 – 473	pmol/L
o	**Testosterone, Total**					
o	*Male*	Blood			6 – 28	nmol/L
o	*Female*	Blood			0.4 – 2.1	nmol/L
o	**TPO Antibodies**	Blood			Negative	
o	**TSH** (*>2 yrs*)	Blood			0.5 – 5.0	mIU/L
o	**HbA1c**	Blood			<6.2 (Normal); >6.5 (Diabetic)	%
o	**Insulin, Fasting**	Blood			2 – 10	mU/L
o	**Glucose, Fasting**	Blood			3.0 – 6.0	mmol/L
o	**Cholesterol**	Blood			<5.6	mmol/L
o	**Triglyceride**	Blood			<2.0	mmol/L
o	**HDL**	Blood			>1.0	mmol/L
o	**LDL**	Blood			<2.5	mmol/L

Case Study 1: Summary



SECTION X: Male Hypogonadism and Sexual Dysfunction

As men age, muscle mass decreases, skin and hair thin, and sex drive decreases. Various symptoms and chronic conditions develop:

- Hypertension (Eizenberg et al., 2016)
- Insulin resistance (Barzali & Ferrucci, 2012; Singh et al., 2013)
- High cholesterol (Singh et al., 2013)
- Depression (Sibillie, 2013)
- Erectile dysfunction (Tirado et al., 2016)
- Urinary urgency (DuBeau, 2006)
- Benign prostatic hypertrophy (Corona et al., 2014)

Testosterone deficiency is often forgotten as a cause to many of these symptoms and conditions. Re-establishing testosterone levels can often ameliorate these conditions. That being said, it is important to note that erectile dysfunction is primarily linked to vascular dysfunction as opposed to low circulating testosterone levels (Shamloul & Ghanem, 2013). Common (non-testosterone) medications used to treat patients with these conditions and symptoms include:

- Anti-hypertensive medications for cholesterol
- 5-alpha reductase inhibitors for benign prostatic hypertrophy
- Antidepressants for affective disorder

The Challenge

- Anti-hypertensive medication
  - Reduce blood perfusion to penis, reducing erection firmness (Manolis & Doumas, 2012)
  - Cholesterol suppression results in decreased endogenous testosterone production (Kelly & Jones, 2014)

- 5-α reductase inhibitors
  - Reduces DHT production resulting in decreased libido (Gur et al., 2013)

Selective-serotonin reuptake inhibitors
  - Decreases libido and delays of inhibits, altogether, ejaculation (Hatzimouratidis et al., 2010)

Men who have excessive body fat may have increased aromatase activity resulting in increased oestrogen levels (Jones et al., 2000). Aromatase is an enzyme responsible for converting testosterone into oestrogen. High aromatase levels results in higher oestrogen to testosterone ratios. Increased oestrogen is linked to decreased insulin sensitivity and blood glucose intolerances. Therefore, oestrogen reduction is necessary for androgen restoration.

Treatment Options

- Weight reduction
- Aromatase inhibition
- Increased oestrogen excretion
- Nutritional considerations to control SHBG levels

Specific Symptoms of Hormone Imbalances in Males

Increased Insulin in Male	Increased Oestrogen in Males	Decreased Oestrogen in Males
Constipation Cravings for Sweet Hot Flashes Hypoglycaemia Increased Facial and / or Body Hair Numbness Hands and Feet Weight Gain: Waist	Anxiety/Nervousness Apathy Bone Loss Burned Out Feeling Decreased Morning Erections Decreased Muscle Mass Decreased Sex Drive Fluid Retention Extremities Prostate Enlargement Urinary Retention Urinary Urgency	Cold Extremities Confusion Decreased Concentration
Increased Testosterone in Male	**Decreased Testosterone in Male**	
Decreased Concentration Hair Loss	Decreased Sex Drive Cold Extremities Apathy Bone Loss Burned Out Feeling Decreased Morning Erections Decreased Muscle Mass Urinary Retention Urinary Urgency	Allergies/asthma Decreased Stamina Fatigue High Cholesterol / Triglycerides Joint Pains Muscle Pain Thinning Skin Tired But Wired
Increased DHEA in Male	**Decreased DHEA in Male**	
Anxiety / Nervousness Tired and Wired	Allergies/asthma Apathy Burned Out Feeling Decreased Morning Erections Decreased Muscle Mass Decreased Sex Drive Decreased Stamina Fatigue High Cholesterol / Triglycerides Joint Pains Muscle Pain Salt Craving Thinning Skin Tired But Wired	

Treatment Protocols for Andropause

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Andropause	PO	Anastrozole	0.1 mg - 0.25 mg (3 times / week) or 0.5 mg (qod)	Aromatase inhibitors block the enzyme aromatase that converts testosterone into oestradiol. Decreasing oestrogens can sometimes be as effective as replacing testosterone.
	Sublingual Buccal	Anastrozole	0.1 mg (qd)	High oestrogens can enhance the negative feedback loop to hypothalamus thus decreasing GnRH secretion and decreasing LH release from pituitary decreasing its stimulation of testosterone from Leydig cells.
	IM	HCG	500 IU (3 - 5 times / week) or 1000 IU - 2000 IU (2 - 3 times / week)	Used only when testes are functional. HCG contains a sub-unit that is same as one of LH resulting in the stimulation of testosterone production by Leydig cells.
	PO	DHEA	15 mg – 75 mg	Pro-hormone, must be converted to other androgens. Oral bioavailability approx. 50%
	Topical	DHEA	10 mg – 50 mg	Bio-availability ~ 85 - 90 %.
	Topical	Progesterone	2 mg – 8 mg (q am)	Progesterone prevents the body from converting testosterone to DHT by inhibiting the enzyme 5-alpha reductase.
	IM	Testosterone	50 mg – 400 mg (q 2 - 4 weeks) 75 mg -100 mg (q week) 150 mg - 200 mg (q 2 weeks)	IM can possibly increase oestradiol conversion during initial peak amount worsening E/T ratio.
	Topical	Testosterone	25 mg - 200 mg (q am)	Prior to initiation, obtain baseline free and total testosterone and oestrogen levels.

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Note: anastrozole is only indicated by the TGA for breast cancer treatment. Use in men for andropause would be off label prescribing

Treatment Protocols for Hypogonadism

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Hypogonadism	IM	HCG	1000 IU - 2000 IU	2-3 times / week Used only when testes are functional. HCG contains a sub-unit that is same as one of LH resulting in the stimulation of testosterone production by Leydig cells.
	IM	Testosterone	50 mg - 400 mg (q 2 - 4 weeks) 75 mg - 100 mg (q week) 150 - 200 mg (q 2 weeks)	IM can possibly increase oestradiol conversion during initial peak amount worsening Oestrogen-to-Testosterone ratio.
	PO	Anastrozole	0.1 mg - 0.25 mg (3 times / week) or 0.5 mg qod	Aromatase inhibitors block the enzyme aromatase that converts testosterone into estradiol. Decreasing estrogens can sometimes be as effective as replacing testosterone.
	Sublingual Buccal	Anastrozole	0.1 mg qd	High oestrogens can enhance the negative feedback loop to hypothalamus. This decreases GnRH secretion and decreases LH release from pituitary, decreasing its stimulation of testosterone from leydig cells.
	Topical	Testosterone	25 mg - 200 mg q am	Prior to initiation, obtain baseline free and total testosterone, and oestrogen levels.

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Note: anastrozole is only indicated by the TGA for breast cancer treatment. Use in men for hypogonadism would be off label prescribing

Treatment Protocols for Erectile Dysfunction

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Erectile Dysfunction	PO	Yohimbine	5.4 mg (tid)	If side effects present, then decrease to 2.7 mg tid
	Sublingual Buccal	Apomorphine	1 mg – 4 mg (daily)	Dopamine agonist; side effects, nausea, dizziness and headache.
	Intranasal	Apomorphine	2 mg - 3 mg	Administer daily
	Transurethral	Papaverine Phentolamine Alprostadil	30 mg 2 mg 40 mcg	Must protect partner from exposure; ex: condom
	Sublingual Buccal	Testosterone	10 mg - 50 mg	Dissolve 30 minutes prior to sexual activity
	Intracavernosal Injection	Alprostadil	5 mcg - 40 mcg	
	Intracavernosal Injection	Papaverine Phentolamine	20 mg – 60 mg 1 mg – 5 mg	Papaverine concentration > 75 mg/mL can crystallize
	Intracavernosal Injection	Papaverine Phentolamine Alprostadil	20 mg – 60 mg 1 mg – 5 mg 5 mcg – 20 mcg	Alprostadil can cause discomfort upon injection

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Note: PDE5 inhibitors are first line for erectile dysfunction. The agents listed here would be considered second or third line.

CASE STUDY 2

Case Description:

Bob has recently undergone some weight gain, decreased sexual interest, depression, hypertension, increased LDL, and decreased HDL. He is reluctant to have a consultation, but his wife who is a client of yours is pushing him to proceed.

Instructions:

1. Work in your small groups.
2. Review all the details provided to you in the case.
3. Use any and all seminar-related tools and charts to help establish a treatment plan.
4. Apply the fundamental principles of hormone therapy and rules of engagement.
5. Determine the tests to be performed and what may be incorrect with current treatment plan.
6. Discuss a *traditional* pharmacotherapeutic plan based on customary practices and standards
7. Discuss a *personalised non-traditional* pharmacotherapeutic plan by taking into account a more appropriate dose, dosage form, route of delivery, and delivery system.
8. Discuss possible *complimentary* therapies.
9. Discuss the risks and benefits or your therapeutic plans.
10. Prepare to provide a verbal summation of the following:
    - Hormone-related abnormalities
    - Rules of engagement followed and fundamental principles respected
    - Traditional pharmacotherapeutic plan
    - Non-traditional pharmacotherapeutic plan: Drug agent selection, route of delivery, and delivery system.
    - Complimentary therapy
    - Risk ← → Benefit assessment for traditional and non-traditional pharmacotherapeutic plans

The Hypothalamic-Pituitary-Thyroid (HPT) Axis

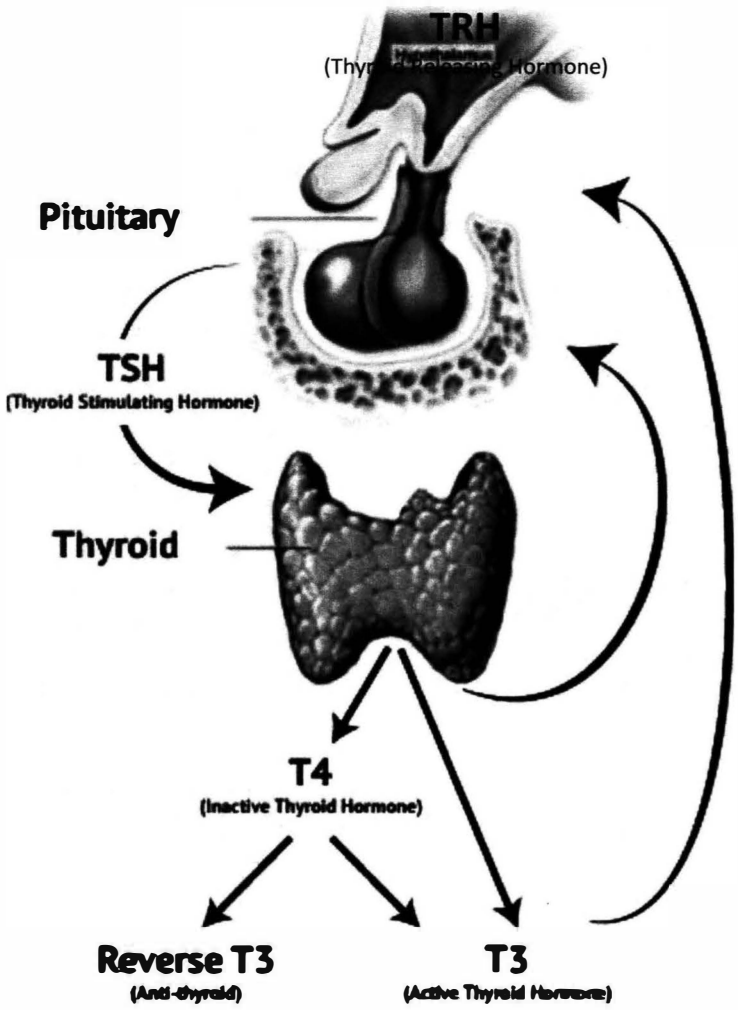


Figure 11. Hypothalamic-Pituitary-Thyroid axis

TRH and **TSH** control systemic availability of T3 and T4, and T3 and T4 ultimately regulate TRH and TSH levels through negative feedback loops

- T4 and T3 levels decrease, TRH and TSH increase
- T4 and T3 levels increase, TRH and TSH decrease

The **hypothalamic-pituitary-thyroid** (HPT) axis plays an integral role in maintaining metabolic homeostasis through a cascade of hormone signals and negative feedback loops.

At the beginning or centre of this cascade is thyroid-releasing hormone (TRH), which is released by the hypothalamus where it travels to the pituitary to stimulate the secretion of thyroid stimulating hormone (TSH). TSH then travels to the thyroid gland to stimulate the release of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) (Biondi & Wartofsky, 2012; Shroeder & Privalsky, 2016).

T4 is exclusively synthesized (iodine required) and secreted by the thyroid gland. T4 is considered a prohormone where it is taken up by extra-thyroidal tissue to be converted into active T3 or inactive reverse T3 (rT3). Under certain stressors (e.g., pregnancy, caloric restriction, emotional stress, chronic illness), T4 metabolism favours the synthesis of rT3. In circulation, T4 (and T3) binds to thyroxine-binding globulin (TBG) with an affinity that is 20-folds higher than the affinity of T3 to TBG (Biondi &Wartofsky, 2012; Koulouri et al., 2013).

T3 is predominately synthesized in extra-thyroidal tissue (80% is secreted by extra-thyroidal tissue and 20% is secreted by the thyroid). T3 is considerably more active than T4 with a 10- to 20-fold greater affinity to thyroid receptors (TR) than that of T4. T3 availability, however, depends highly on deiodinase activity, which is responsible for converting T4 into T3. Deiodinase Type 1 is responsible for peripheral conversion and Deiodinase Type 2 is responsible for hypothalamic and pituitary conversion. (Biondi &Wartofsky, 2012; Koulouri et al., 2013).

Thyroid Hormone Metabolism

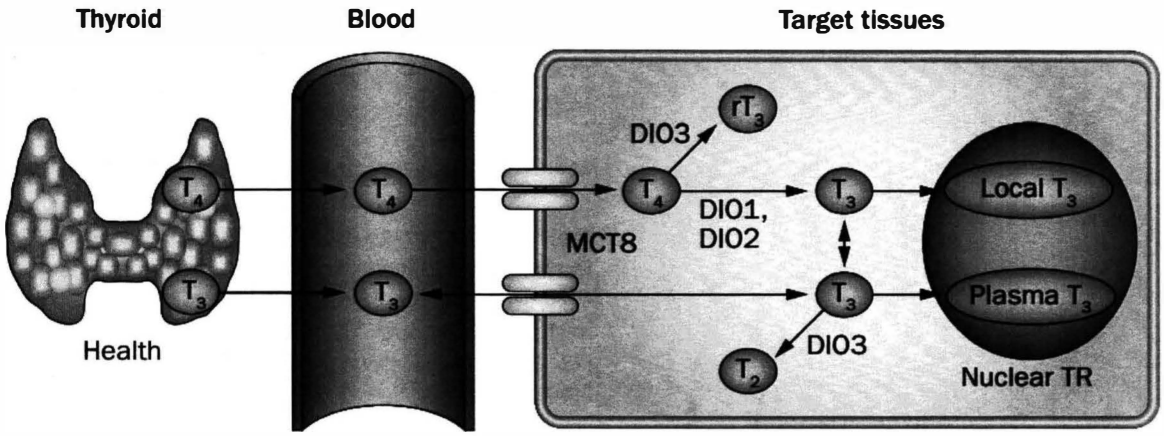


Figure 12. Peripheral target and metabolism of thyroid hormones

In the case of hypothyroidism – **Treat the adrenals**

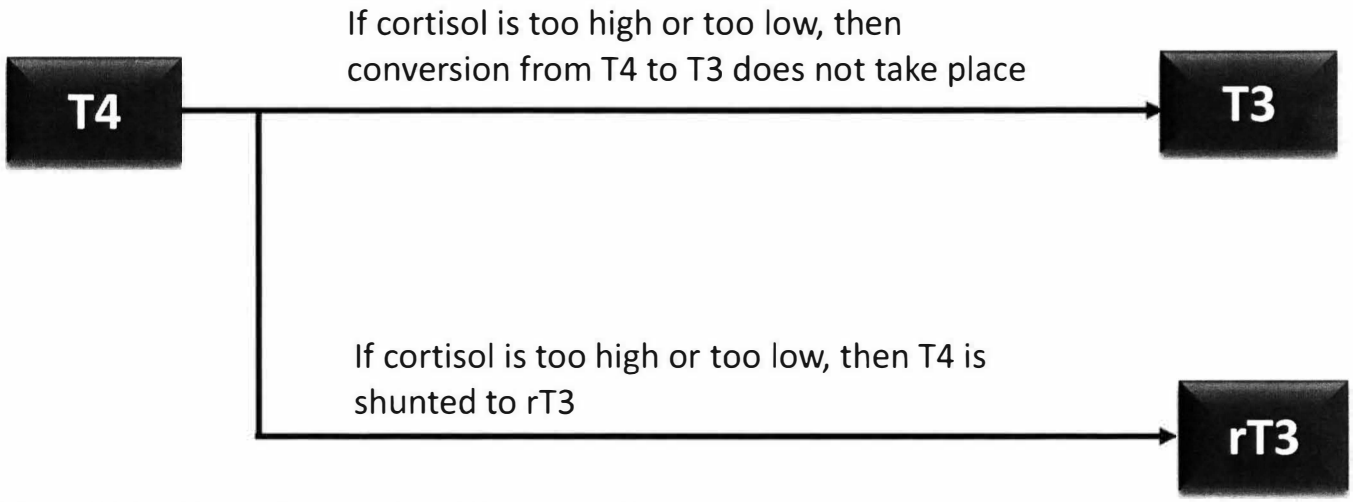


Figure 13. Thyroid hormone conversion relative to cortisol levels

Factors that Disrupt T4 to T3 Conversion		
Nutrient Deficiencies	**Medications**	**Other Factors**
Selenium(Lin et al., 2014)	Glucocorticoids(Greenen, 2016)	Aging(Donda & Lemarchand-Beraud, 1989)
Chromium(Larson & Berry, 1995)	Beta-Blockers(Greenen, 2016)	Alcohol(McGregor, 2015)
Iron(Prasad, 2013)	Oral Contraceptives / HRT(Awad, 2015)	Smoking(McGregor, 2015)
Copper(Larson & Berry, 1995)	SSRIs(Greenen, 2016)	Diabetes(Hashizume, 2013)
Zinc(Maxwell & Volpe, 2007)	Opiates(Ilias et al., 2001)	Growth hormone deficiency(Burman et al., 1996)
Iodine(Larson & Berry, 1995)	Amiodarone(Greenen, 2016)	Low Adrenal function(Wilson, 2015)
Vitamin A(Larson & Berry, 1995)	Chemotherapy(Geffner et al., 1975)	Mercury(Wilson, 2015)
Vitamins B2, B6, B12(Stokstad et al., 1980)	Lithium(Greenen, 2016)	Pesticides(Campos & Freire, 2016)
Vitamin D(Alrefaie & Awad, 2015)	Lithium(Thut & Cheng, 2013)	Stress; excessive cortisol(McGregor, 2015)
		Surgery or Radiation(Hajioun et al., 2014)
		Weight loss(Agnihothri, 2014)
		Liver and kidney disease(Lim, 2001)

Inter-Hormone Relationships and Thyroid Function

Inter-Hormone Relationships and Thyroid Function: Special Considerations and Recommended Treatments		
Hormone	**Resultant Effect**	**Treatment Parameter**
TSH Low & T4 High	Inverse relationship created by negative feedback loop.	
TSH Low & T3 High	Inverse relationship created by negative feedback loop.	
Cortisol High & T3 Low	Increased cortisol inhibits 5'deoidinase that converts T4 to T3; instead goes to RT3.	Patient may have symptoms of low thyroid with normal T4 levels and TSH. Need to check free T3.
Cortisol High & TSH Low	High cortisol inhibits the production of TSH in pituitary.	Patient may have symptoms of low thyroid with normal T4 levels and TSH.
Cortisol Low & T3 Low	T4 is unable to convert to T3 without cortisol.	If cortisol is low, must check T3. Treat adrenals first. May need to treat with Cortef before you are able to give T4/T3.
Vitamin D Low & TSH, T4 Normal	Low Vitamin D causes the target tissues to be less responsive to thyroid hormones.	Vitamin D needs to be 50-70. Patient may have normal thyroid lab values but symptoms of hypothyroid.
rT3 High & T3 Low	Excess rT3 occupies receptor but can't activate it. T4 level may be normal.	Patient will have symptoms of hypothyroid but labs do not correspond unless you check rT3.

Thyroid Dysfunctions

Decreased Thyroid Activity

Like the adrenal gland the thyroid has activities that encompass virtually all of the other endocrine glands. All cells in the body have thyroid receptors. When thyroid levels are low, often a person feels very poorly.

- Decreased thyroid hormone activity in the presence of normal thyroid hormone levels can be caused by low or high cortisol levels; both hormones are needed for optimal energy and metabolic activity.
- Symptoms of progesterone deficiency and decreased thyroid activity can be very similar. Progesterone is anabolic (burns fat) and thermogenic (increases temperature) so that a deficiency causes weight gain and low temperature.
- Progesterone can improve thyroid activity by improving or eliminating oestrogen dominance. Excess oestrogen can increase thyroid binding globulin synthesis thus binding thyroid hormone and decreasing its activities.
- Synthetic progestins decrease thyroid hormone function. Progestin blocks progesterone receptors and prevents biomimetic progesterone from modulating its normal activity such as decreasing oestrogen dominance. Common monographs for synthetic progestins list fatigue and loss of energy as common side effects.

Hypothyroidism

Features:

- Clinical condition characterized by reduced production of T4 and T3
- Correlated with aging; thyroid function decreases with age
- Could be due to lack of components that make up thyroid hormone; Iodine and tyrosine deficiency
- Could be due to poor recovery following acute stress
- Associated with low basal body temperature in the morning

Treatment Protocols for Hypothyroid

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Hypothyroidism	PO	Combination T3 / T4	Start with T3 - 5 mcg, adjust up according to labs Start with T4 - 25 mcg, adjust up according to labs	Avoid lactose as excipient; delays absorption. Can combine compound with selenium, chromium or hydrocortisone.
	PO-SR	Combination T3 / T4	Start with T3 - 5 mcg, adjust accordingly Start with T4 - 25 mcg, adjust accordingly	Take on an empty stomach. SR formulations allow for higher dosing with minimal systemic effects.
	PO	Individual T3 or T4	Start with T3 - 5 mcg Start with T4 - 25 mcg	
	PO-SR	Individual T3 or T4	Start with T3 - 5 mcg Start with T4 - 25 mcg	
	PO	Thyroid USP	Start with T3 - 5 mcg Start with T4 - 25 mcg	
	PO / Drops	Iodine (Lugol's Solution)	Multiple dosing	For iodine deficiency

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

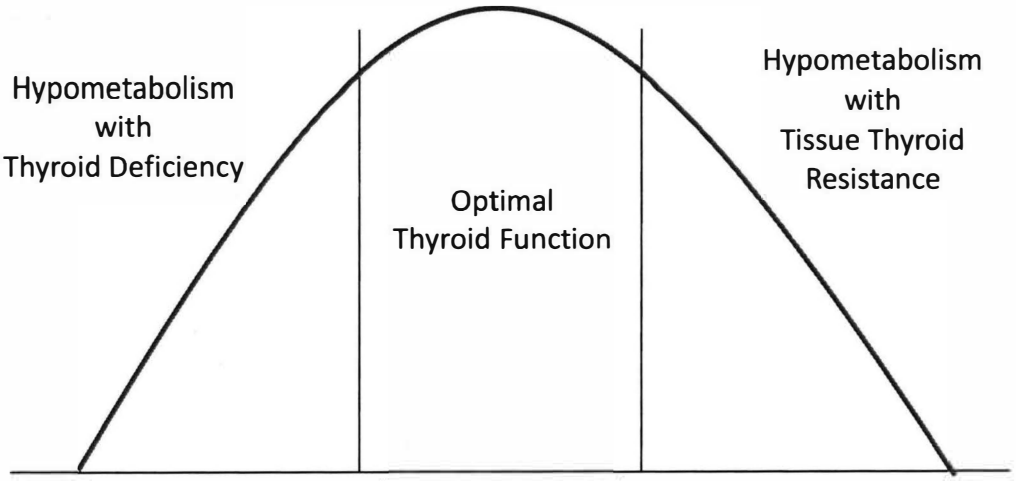
Dosages for T3: Start at 5 mcg; make increments depending on subsequent testing.
Dosages for T4: Start at 25 mcg; make increments as necessary.

Specific Symptoms Associated with Increased Insulin and Decreased Thyroid

Increased Insulin	Decreased Thyroid	
Cravings for Sweet	**Cold Body Temperature**	Breast Tenderness
Hypoglycaemia	**Cold Extremities**	Confusion
Weight Gain: Waist	**Constipation**	Decreased Sex Drive
Hot Flashes	**Decreased Stamina**	Deepening of Voice
Constipation	**Dry Skin / Hair**	Headaches
Increased Facial and / or Body Hair	**Fatigue**	Heart Palpitations
Numbness Hands and Feet	**Increased Hair Loss**	Hot Flashes
	Weight Gain: Hips	Joint Pains
	Weight Gain: Waist	Muscle Pain
	Brittle Nails	Sleep Disturbances
	Burned Out Feeling	Cramping Abdominal
	Decreased Concentration	Decreased Sexual Sensation
	Depressed Mood	Tired But Wired
	Dry Eyes	
	Fibrocystic Breasts	
	Fluid Retention Extremities	
	Foggy Thinking	
	Heavy & Irregular Menses	
	Hoarseness	
	Night Sweats	
	Swollen Eyes	
	Thinning Skin	

Functional Hypometabolism

In this case, thyroid levels are optimal in values and relationship to each other, but symptoms persist. Thyroid receptors are not responding to optimal thyroid level and target tissues of the body have reduced responsiveness to thyroid hormone.



Causation related to Hypo-metabolism:

- Low range of Vitamin D
- Impaired T3 transport
- Low ferritin; optimal level is 90-110
- Chronic low cortisol
- High rT3
- High TPO
- Autoimmune antibodies

Causation related to Functional Hypo-metabolism:

- Genetic abnormalities of the thyroid hormone receptor
- Autoimmune or toxic damage to the thyroid hormone receptor
- Competitive binding to receptor by pollutants, food additives
- Excessive competitor to T3:
    - Progesterone, Vitamin D, Omega 3 Fatty acids
    - Excess of any can block signalling of the others
- Excess Cortisol:
    - Inhibits T4 to T3 conversion
    - Suppresses TSH
    - Decreases thyroid receptor responsiveness
- Low Cortisol:
    - Decreases thyroid receptor responsiveness
    - May inhibit T4 to T3 conversion
    - Transport across the membrane is energy dependent & modified by cortisol
    - Cortisol regulates T3 receptor density
    - May have to give cortisol to make thyroid supplementation work properly

Vulvar and Vaginal Atrophy

Vulvar and vaginal atrophy is a chronic condition typically experienced in postmenopausal women. Indeed, up to 50% of postmenopausal woman report symptoms of vaginal atrophy; numbers that are expected to grow with the aging population (Kinsberg et al., 2013). Vaginal atrophy is characterized by thinning of the epithelial lining of the vagina and lower genitourinary tract, drying and inflammation of the vaginal walls, and loss of vaginal elasticity (Kinsberg et al., 2013). These changes in the vaginal environment are most commonly associated with symptoms of dyspareunia (i.e., pain during intercourse) and irritation. As one can imagine, symptoms of vaginal atrophy can significantly impede sexual activities, relationships, and overall quality of life.

Unfortunately, an *overwhelming* number of women experiencing vaginal atrophy are left untreated. Indeed, of the estimated 32 million women suffering from vaginal atrophy in the United States, only 2.3 million (7%) are currently being treated with prescription medications (Mac Bride, 2010). Factors contributing to this dramatically high number in women left untreated can be attributed in part to inadequate identification of vaginal atrophy by practitioners, patients not seeking treatment, and the current limited therapeutic options commercially available (Kingsberg et al., 2013).

Treatment Protocol for Vulvar and Vaginal Atrophy

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Vaginal Atrophy	Topical	Oestriol DHEA	0.25 mg – 1.5 mg 1 mg – 4 mg	Can compound multiple combinations with Vitamin E, Testosterone
	Vaginal Insert	Oestriol	0.25 mg – 1.5 mg	Can compound multiple combinations with Vitamin E, Testosterone
	Topical	Oestriol Vitamin E	0.25 mg – 1.5 mg 100 IU - 400 IU	
	Vaginal Insert	Oestriol Vitamin E	0.25 mg – 1.5 mg 100-400 IU	
	Topical	Testosterone	0.1 mg – 0.4 mg	
	Topical	Retinoic Acid	0.05 % - 0.4 %	
	Vaginal Insert	Oestradiol in combination with...	Multiple dosages	Potential combinations with progesterone, Vitamin E, Testosterone

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Vulvodynia

Vulvodynia is chronic pain in vulvar region without identifiable cause. Vulvodynia can be classified into localized vulvodynia and generalized vulvodynia. Women with localized vulvodynia typically experience provoked vestibulodynia (PVD), which refers to pain that arises in the vestibule area (i.e., tissue surrounding the vaginal opening) when pressure is applied. Sources of pressure include sexual intercourse, tampon insertion, gynaecological exams, sitting for prolonged periods, and wearing fitted pants. Localized PVD can be further classified into primary PVD (i.e., pain that is experienced from first-intercourse forward) and secondary PVD (i.e., pain that emerges later in life, after normal intercourse experiences). In rare cases localized vulvodynia can affect the clitoris and is referred to as clitorodynia. Generalized vulvodynia (GVD) occurs spontaneously without identifiable cause or pressure and is relatively constant with few periods of relief. Pressure can typically exacerbate the pain symptoms (National Vulvodynia Association, 2017).

Vulvodynia is multifaceted and complex, involving both physical and psychological factors. Additionally, vulvodynia pain experience is often unique, varying from individual to individual. Treating vulvodynia typically involves a trial and error approach until an effective therapeutic is achieved. Given the complexity and individuality of vulvar pain, customised therapeutics tailored to the individual patient's needs are strongly warranted.

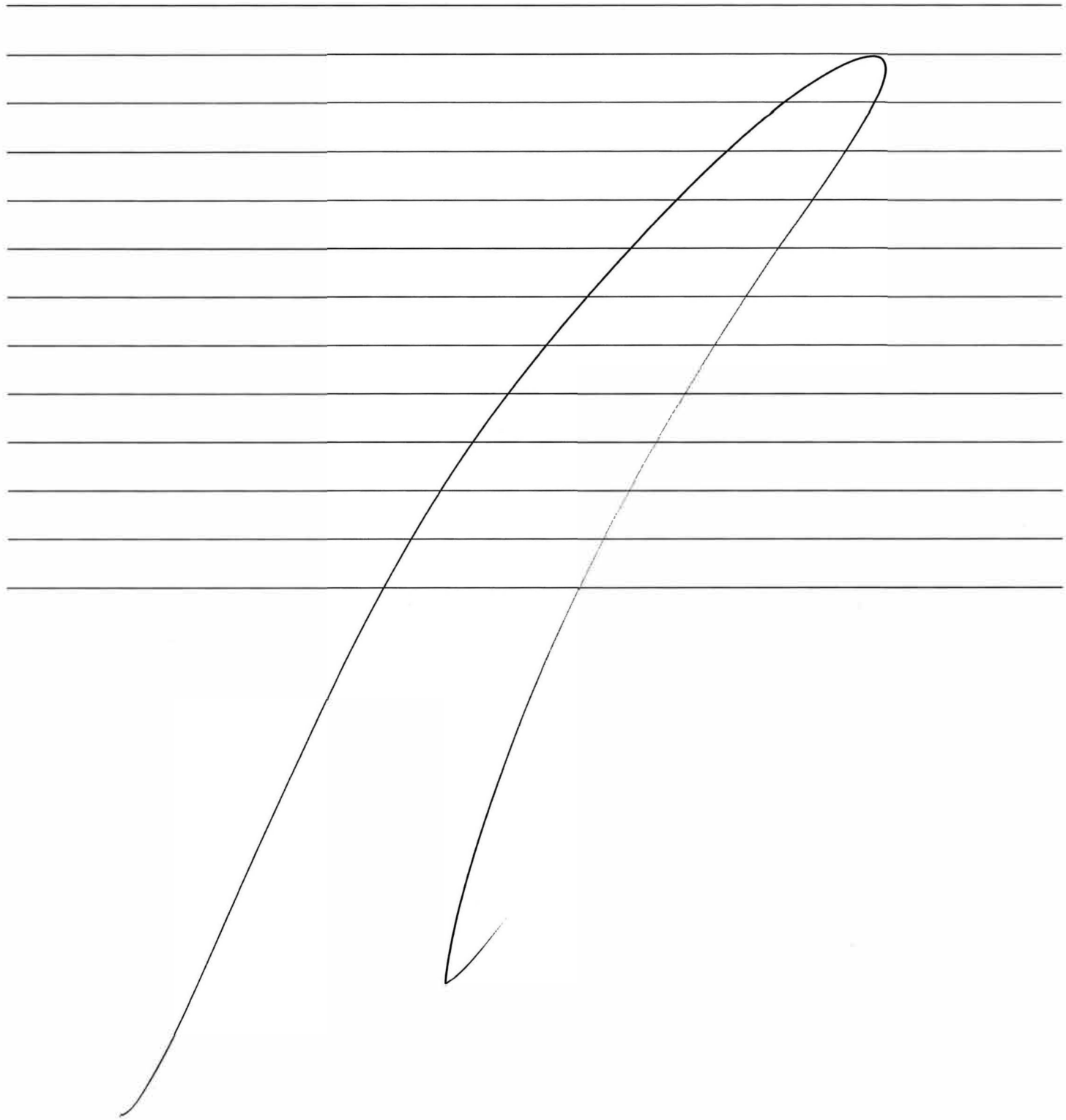
Treatment Protocol for Vulvodynia

Condition	Route	Drug Agent	Initial Range	Special Instruction / Circumstance
Vulvodynia	Vaginal Cream	Gabapentin	4% – 8%	Combinations with benzocaine, oestrogen, baclofen, etc...
	Vaginal Suppository	Atropine	0.20% - 0.25%	Decreases excess stimulation of pelvic floor muscles
	Vaginal Cream	Oestradiol or Oestriol	0.01% - 0.05% or 0.25% - 1.0%	Hydrophilic petrolatum base Can combine with benzocaine or baclofen or gabapentin
	Topical Hydrophilic Petrolatum	Baclofen	2%	Multiple combinations possible
	Topical Hydrophilic Petrolatum	Ketamine	4% - 6%	
	Topical Hydrophilic Petrolatum	Lidocaine Benzocaine	5% 10%	

Table adapted from Rakel, D. (2012). Integrative medicine. Elsevier Health Sciences.

Note: Baclofen is only indicated by the TGA for the suppression of voluntary muscle spasm e.g. in multiple sclerosis, and ketamine is indicated for anaesthesia. Use of these agents for vulvodynia would be off label prescribing

Case Study 4: Summary



Testosterone-Specific Facts Related to Females

- Always consider testosterone levels in women with surgical menopause.
- Women with very high stress or known adrenal issues are usually low in testosterone and DHEA (the source of androgens for the postmenopausal patient).
- Transdermal delivery is better.
- Should always test levels before prescribing.
- Can use salivary or serum for testing and monitoring.
- Testosterone is produced 25% by ovary, 25% by adrenal gland, 50% by peripheral conversion.
- If testing serum levels, must order a free level and it must be drawn in the morning; there is a diurnal variation.
- Re-test after initiating progesterone; many women have a 10–20 pg/mL (37-74 pmol/mL) elevation in salivary testosterone when using topical progesterone.
- Consider DHEA if both testosterone and DHEA are low.
- Oral DHEA can raise testosterone levels by 50%, and provides immunological benefits that testosterone alone does not.
- High doses of DHEA can cause insulin resistance.

SECTION XIII: Strategies for Treatment Modification

Detoxification from Excessive Hormone Therapy

High Oestradiol from Exogenous Sources:

- This is usually seen with a patient taking synthetic oral oestrogen who wants to convert to biomimetic hormones.
- First the dosage of synthetic needs to be weaned. When the patient reaches around 0.625 mg conjugated equine oestrogen or the equivalent, they can be converted to an oestradiol patch 0.05 mg to provide steadier dosing of biomimetic oestradiol.
- If the patient had not been taking any progesterone as in the case of most patients after hysterectomy, start oral progesterone SR 100 mg q HS first for at least 3-4 weeks before starting to wean oestrogen dose. The progesterone will down regulate the oestrogen receptor.
- After an acceptable dose of oestradiol is reached via patch and the patient's symptoms are better, she can be converted to Biest.
- Supplements such as milk thistle 175 mg BID and omega 3 fatty acids, at least 1000 mg of EPA + DHA, can help to remove oestrogen metabolites from the liver.

High Oestradiol from Endogenous Sources:

- This occurs when either a patient is given oestrogen therapy in the perimenopause for the symptom of hot flashes, or a patient who has had a partial hysterectomy (ovaries remain) and is prescribed oestrogen when her ovaries are still producing oestrogen.
- If the patient has a high level of oestrogen and is not taking any, an ovarian cyst must be ruled out by transvaginal ultrasound.
- If the patient is perimenopause, usually you can just have them stop the oestrogen prescription as they are still producing enough oestrogen.
- Supplements such as milk thistle and omega 3 fatty acids should be suggested.

High Progesterone from Exogenous Sources:

- If the patient is still cycling, usually they can tolerate a reduction by 50%. They should stop taking it all together on days 1-14.
- If the patient is postmenopausal, they will need to be weaned more slowly.
- Some patients may tolerate stopping progesterone completely for 2 - 4 weeks to let the body get rid of excess naturally.

High Testosterone from Exogenous Sources:

- Testosterone can be held for 2-4 weeks, or the dose can be reduced by 50% depending on the patient's symptoms.
- If it is from endogenous production, Spironolactone 50 mg q HS or BID can act as a testosterone blocker as the patient normalizes.
- Saw palmetto 160 mg also helps to block the conversion from testosterone to DHT via 5-alpha reductase in the periphery.

Discontinuation from Conjugated Oral Oestrogens

If a female patient wants to discontinue conjugated oral oestrogens (CEE), it should be done slowly to minimize symptoms and rebound effects.

If vasomotor symptoms occur and are bothersome instruct the patient to return to the previous level for one additional week then continue.

Step-wise Process (Assumes patient is taking dose daily):

- Start tapering off by taking one oestrogen dosage every other day for two weeks.
- Continue tapering with one dosage unit tablet twice a week for one month.
- Take one dosage unit weekly for 2 - 3 weeks, and then discontinue
- During the above mentioned time frame, topical progesterone may be administered to diminish some oestrogen withdrawal symptoms.

Discontinuation from Conjugated Oral Oestrogens and Initiation of Compounded Oestrogen

If a female patient wants to discontinue conjugated oral oestrogens (CEE) and initiate a topical compounded oestrogen preparation, the process of weaning off oral CEE should be done slowly to minimize symptoms and rebound effects. If vasomotor symptoms occur and are bothersome instruct the patient to return to the previous level for one additional week then continue.

Step-wise Process (Assumes patient is taking dose daily):

- Initiate progesterone at the appropriate starting dose.
- Start tapering off by taking one oestrogen dosage every other day for one week.
- After one week of tapering off CEE, initiate a daily dose of a topical compounded oestrogen at an initial low starting dose.
- Continue tapering off with one CEE dosage unit tablet twice a week for two weeks.
- Continue tapering off CEE by taking one dosage unit weekly for two weeks, and then discontinue.

End of Treatment Strategy – Female

If a female patient wants to discontinue hormone therapy, it should be done slowly to minimize symptoms and rebound effects. If vasomotor symptoms occur and are bothersome instruct the patient to return to the previous level for one additional week then continue.

If oestrogen is transdermal:

- Decrease oestrogen dose by ≈ 25% every week until dose is at 25% of the dose prior to beginning
- Administer lowest oestrogen dose every other day for two weeks
- Administer lowest oestrogen dose every third day for two weeks
- Administer lowest oestrogen dose weekly for one week
- Administration is now complete; oestrogen dosing terminated

If oestrogen is oral or transmucosal; assumes patient is taking dose daily:

- Start taper by taking one oestrogen dosage every other day for two weeks
- Continue tapering with one dosage unit tablet twice a week for one month
- To conclude, take one dosage unit weekly for 2 - 3 weeks then discontinue

Delivery Device

A drug **delivery device** is a device that enables and can enhance the administration and/or introduction of an API in the body thus potentially improving its efficacy and safety by controlling the amount, use, and exposure of drug during the administration process.

Group Discussion / Interactive Activity

- Instructions: In your small groups discuss some considerations when selecting a specific drug delivery device. Be prepared to share your findings with the large group.

Drug Delivery Device	General Consideration(s)
Metered dose pumps	
Metered dose syringes	
Metered dose pens	
Vaginal applicators	
Others?	

Special Considerations

Factors Affecting Percutaneous Absorption:

- Increased lipophilicity results in increased penetration of stratum corneum
- Less ionized drugs are better absorbed
- The thicker the stratum corneum, the more slowly the drug is absorbed
- A drug must partition from delivery system, in order to be absorbed
- Hydrated skin improves absorption
- Elevated temperature increases absorption
- The greater the flow to the site of absorption, the greater the potential for absorption
- Percutaneous enhancing agent increases absorption
- Site of absorption often forms depots
- Great inter-patient variability in absorption
- Great inter-site variability in absorption. Some rules to follow include:
    - Apply to inner thigh, back of arm, lower abdomen
    - Avoid back of knee, buttocks, neck and throat
    - Rotate sites
    - Rub in well for at least one minute
    - Be careful to avoid possible transfer of hormone to others

Factors Affecting Buccal / Sublingual Absorption:

- Absorption surface is small 200 cm^2
- Rich in blood and lymphatic vessels so fast absorption is likely
- pH of area 6.2 - 7.4
- Mostly by-pass first pass effect; though there is some metabolism via mucosa and salivary glands
- Tablets are better absorbed than liquids due to less dilution with saliva
- Taste is an important factor as some patients get very nauseous with certain tastes
- Swallowing also occurs with this route

Formulating Related Considerations:

- API solubility
    - Mill/EMP
- Melting point
- Weight/Weight vs Weight/Volume
- Dispensing device calibration
- Internal and External QC
- Packaging

Additional Considerations:

- Partition co-efficient is an expression of a drug agent's ability to leave a delivery system
- Relationship between partition co-efficient and dosing schedules
- Relationship between local effects and skin hydration, peripheral circulation, skin condition and skin thickness
- Relationship between systemic effects and hydration, serum protein levels and GI function
- Adequate dosing schedule after establishing the route of delivery
- Evaluation of known pharmacokinetic / pharmacodynamic variables
- Feasibility of pharmacotherapeutic alternative when more than one route of delivery may be appropriate
- Evaluation of convenience, compliance and customization
- Evaluation of side effect profile
- Evaluation of physical and chemical properties of drug agent in relation to delivery system's ingredients

SECTION XV: PCOS, Metabolic Syndrome, and Insulin Resistance

Polycystic Ovary Syndrome

According to the Rotterdam criteria, the overall prevalence of Polycystic Ovary Syndrome (PCOS) is 16.5% (Lauritsen et al., 2014). Interestingly, the incidence of PCOS significantly diminishes with age, with a prevalence of 33.3% in women less than 30 years, 14.7% in women aged 30 to 24, and 10.2% in women greater than 35 years (Lauritsen et al., 2014). By these reports, PCOS represents the most common endocrine pathology in reproductive women and burdens the US with approximately $4 billion annually in healthcare and lost workforce costs (Conway et al., 2014). PCOS is clinically variable and diverse in nature, with much disagreement on the diagnostic criteria (Conway et al., 2014). Despite relentless disagreements, PCOS typically involve the presence of some or all of the following characteristics

- Clinical hyperandrogenism or high serum androgens
- Annovulation or presence of other ovulatory dysfunction
- Presence of polycystic ovaries on ultrasound

Metabolic Syndrome

Interestingly, many patients with PCOS also experience metabolic dysfunctions including insulin resistance and hyperinsulinaemia, and are often overweight or obese. Given these associations it is suggested that major metabolic disorders, including metabolic syndrome, be addressed in the workup when PCOS is suspected. Metabolic syndrome has some serious long-term sequelae and should be identified as soon as possible. For patients not pursuing fertility but not wanting to prevent it, treatment with hormone therapy is an option. The criteria for metabolic syndrome include:

- Elevated BP > 130/85
- Waist Circumference > 35 inches (89 cm)
- Elevated Fasting glucose > 100 mg/dL (5.5 mmol/L)
- Low HDL < 50 (2.8 mmol/L) ; Elevated TG > 150 (1.7 mmol/L)

Although the hormone imbalance is similar to that seen in the case of perimenopause, it is not unusual for these girls to be asymptomatic. The onset could be so gradual, or they could just be accustomed to the symptoms they have had their whole life.

Laboratory values need to be interpreted correctly as the patient may be in a prolonged follicular phase.

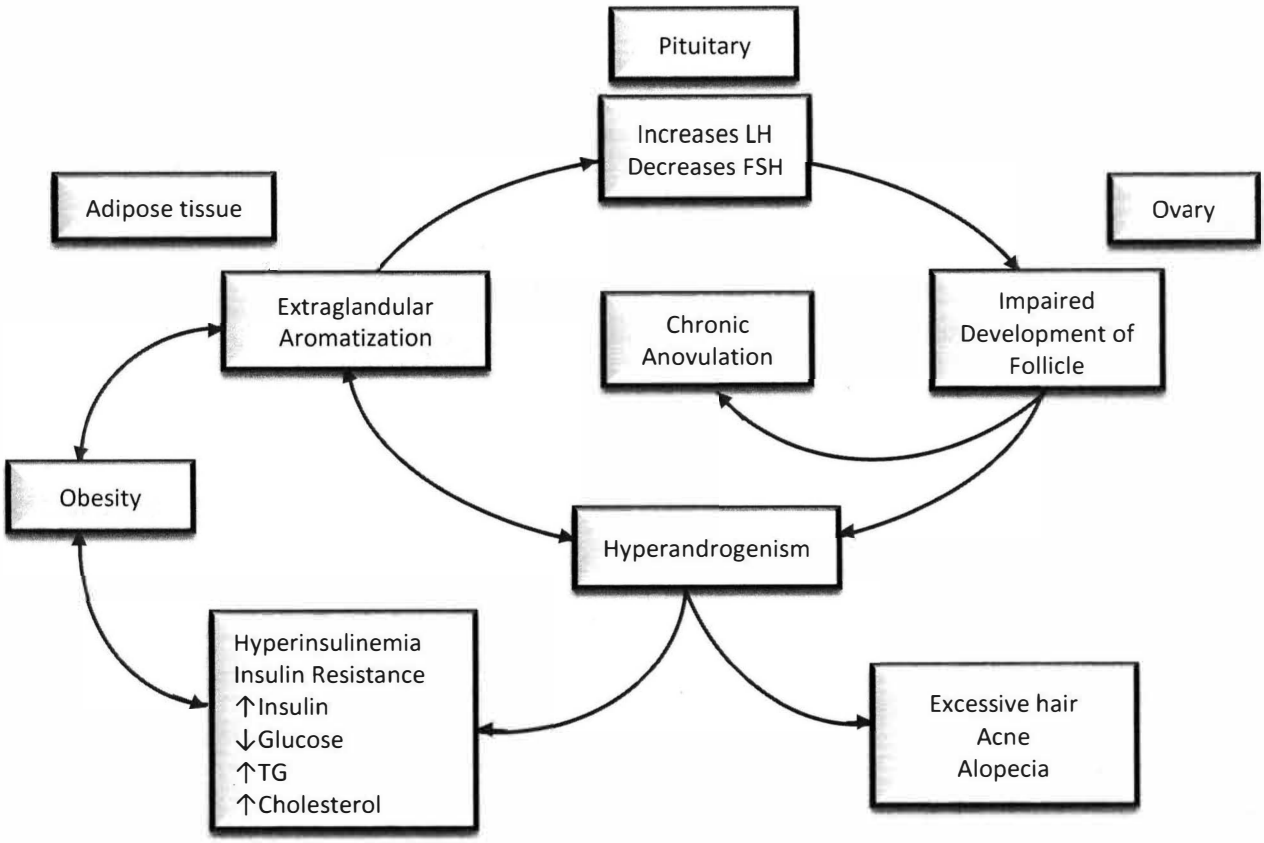


Figure 14. Pathophysiology of polycystic ovary syndrome

CASE STUDY 6

Case Description:

Christy is a single female who is the director of the children's ministry at a large local church. She has devoted her time to her job and has not really taken good care of herself. She admits that she does not have the best diet, but complains of a 40-pound (18 kg) weight gain over the past year. She admits to always having irregular menstrual cycles as long as she can remember. She has not been to a doctor since she got off of her parent's insurance at age 21. The main reason she is seeking medical advice now is for headaches and dizzy spells. She went to her family doctor who wanted to start her on a blood pressure medicine, a cholesterol medicine, and possibly one for her sugar. She would like a more natural approach so she presents for evaluation.

Instructions:

1. Work in your small groups.
2. Review all the details provided to you in the case.
3. Use any and all seminar-related tools and charts to help establish a treatment plan.
4. Apply the fundamental principles of hormone therapy and rules of engagement.
5. Determine the tests to be performed and what may be incorrect with current treatment plan.
6. Discuss a *traditional* pharmacotherapeutic plan based on customary practices and standards
7. Discuss a *personalised non-traditional* pharmacotherapeutic plan by taking into account a more appropriate dose, dosage form, route of delivery, and delivery system.
8. Discuss possible *complimentary* therapies.
9. Discuss the risks and benefits or your therapeutic plans.
10. Prepare to provide a verbal summation of the following:
    - Hormone-related abnormalities
    - Rules of engagement followed and fundamental principles respected
    - Traditional pharmacotherapeutic plan
    - Non-traditional pharmacotherapeutic plan: Drug agent selection, route of delivery, and delivery system.
    - Complimentary therapy
    - Risk ← → Benefit assessment for traditional and non-traditional pharmacotherapeutic plans

Closing Remarks

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Appendix A: Abbreviations

Adrenocorticotropic hormone (ACTH)

Corticotropin-releasing hormone (CRH)

Cortisol (C)

Oestrone (E1)

Oestradiol (E2)

Oestriol (E3)

Dehydroepiandrostenedione (DHEA)

Dihydrotestosterone (DHT)

Follicle Stimulating Hormone (FSH)

Gonadotropin-releasing hormone (GnRH)

Insulin (I)

Luteinizing Hormone (LH)

Progesterone (P)

Testosterone (T)

Thyroid (Th)

Thyroid Stimulating Hormone (TSB)

Thyroxine (T4)

Thyroxine Binding Globulin (TBG)

Thyroxine Binding Pre-albumin (TBPA)

Triiodothyronine (T3)

Sex Hormone Binding Globulin (SHBG)

Appendix B: Hormones and their Primary Function

ACTH (ACTH) (Anterior Pituitary):

- Stimulates glucocorticoid and mineralocorticoid and androgen synthesis and release from adrenocorticoid cells

Aldosterone (Adrenal Cortex):

- Mineralocorticoid
- Regulate salt and water balance

Androgens: DHEA and Testosterone (Adrenal Cortex):

- Masculinization effect in men and women

Androstenedione (Ovary):

- Substrate for oestrogen

Calcitonin (Thyroid):

- Stimulates osteoblasts and bone construction, inhibits Ca2+ release from bone, thus reducing blood calcium

CRH (Hypothalamus):

- Simulate ACTH release from Ant Pituitary

Cortisol (Adrenal Cortex):

- Acts as an anti-inflammatory
- Maintains blood sugar levels, blood pressure and muscle strength
- Helps regulate salt and water balance

Dopamine (Adrenal Medulla):

- Increase heart rate and blood pressure

Dopamine (Hypothalamus):

- Inhibits prolactin release from Anterior pituitary

Epinephrine (Adrenal Medulla):

- Fight or flight response
- Increase heart rate
- Increase oxygen and glucose to brain and muscles
- Suppresses non-emergency bodily processes
- Suppresses immune system

Oestradiol (Testes):

- Prevent Apoptosis of germ cells

Oestrogen (Ovary):

- Promote formation of secondary sex characteristics
- Accelerate height, growth and metabolism
- Burns fat
- Reduce muscle mass
- Increase uterine growth
- Reduce bone resorption
- Increase bone formation

FSH (Anterior Pituitary):

- Stimulates follicular growth in ovaries
- Male: Stimulates spermatogenesis, maturation of seminiferous tubules, and production of androgen binding protein from Sertoli cells of testes

Glucagon (Pancreas):

- Glycogenolysis and gluconeogenesis in liver
- Increases blood glucose level

GnRH (Hypothalamus):

- Stimulate FSH release from anterior pituitary
- Stimulate LH release from anterior pituitary

Growth Hormone (Anterior Pituitary):

- Stimulates growth and cell reproduction
- Stimulates insulin-like growth factor 1 release from liver

Growth Hormone Releasing Hormone (Hypothalamus):

- Stimulates GH release from anterior pituitary

Inhibin (Testes):

- Inhibit production of FSH

Inhibin (Ovary):

- Inhibit production of FSH

Insulin (Pancreas):

- Intake of glucose, glycogenesis and glycolysis in liver and muscle from blood
- Intake of lipids and synthesis of TG in adipocytes
- Other anabolic effects

Insulin-like Growth Factor (somatomedin) (Liver):

- Insulin like effects, regulates cell growth and development

LH (Anterior Pituitary):

- Stimulates ovulation and formation of corpus luteum
- Stimulates testosterone synthesis

Melanocyte Stimulating Hormone (Intermediate Pituitary):

- Stimulates melanin synthesis and release from skin and hair melanocytes

Melatonin (Pineal):

- Antioxidant
- Monitors circadian rhythm and induces drowsiness

Norepinephrine (Adrenal Medulla):

- Fight or flight response
- Increases skeletal muscle readiness

Oxytocin (Hypothalamus):

- Uterine contractions
- Lactation

Oxytocin (Posterior Pituitary):

- Uterine contractions, lactation

Progesterone (Ovary):

- Supports pregnancy
- Raise epidermal growth factor 1 levels
- Increases core temperature during ovulation
- Relaxes smooth muscle
- Reduces gall bladder activity
- Normalizes blood clotting and vascular tone
- Assists in thyroid function

Prolactin (Anterior Pituitary):

- Stimulates milk synthesis and release from mammary glands
- Mediates sexual gratification

PTH (Parathyroid):

- Stimulates calcium and phosphate release from bone; results in increasing blood levels
- Stimulates osteoclasts; breaking down of bone
- Stimulates calcium resorption in kidney
- Stimulates Vitamin D production in kidney

Appendix C: Evidence-Based Medicine Used in Hormone Restoration Therapy

This section highlights a series of research abstracts that clarify misconceptions, provides evidence for program content as well as simply providing a learning experience for the reader. Sub-sections include:

- Risk of Thromboembolism
- Breast Cancer and Hormone therapy
- Progesterone Therapy
- Oestrogen Therapy
- Thyroid
- Androgen Therapy – Testosterone
- Androgen therapy – DHEA
- Cortisol

- **Schmidt, John W. "Hormone replacement therapy in menopausal women: Past problems and future possibilities" *Gynecological Endocrinology,* October 2006; 22(10): 564-577.**

"Oral administration of conjugated equine estrogens (CEE) with and without the synthetic progestin medroxyprogesterone acetate (MPA) in postmenopausal women is associated with side-effects that include increased risk of stroke and breast cancer. The current evidence that transdermal administration of estradiol may provide a safer alternative to orally administered CEE is reviewed. Transdermally administered estradiol has been shown to be an efficacious treatment for hot flushes possibly without the increase in blood clotting that is associated with administration of oral CEE. Further, natural progesterone may have a more beneficial spectrum of physiological effects than synthetic progestins. The substantial differences between CEE compared with estradiol and estriol, as well as the differences between synthetic MPA and natural progesterone, are detailed. Estriol is an increasingly popular alternative hormone therapy used for menopausal symptoms. There is evidence that estriol, by binding preferentially to estrogen receptor-B, may inhibit some of the unwanted effects of estradiol. "

"Relief of hot flushes in postmenopausal women can usually be achieved by maintaining serum estradiol levels at 40-50 pg/ml, the lowest level of estradiol that is expected to be seen in a typical menstrual cycle."

"The rapid metabolism by the liver and the hydrophobic nature of sex steroid hormones suggests that topical administration should be carefully considered as a viable route of administration."

"There are studies that indicate progesterone may have fewer side-effects than synthetic progestins."

"Several lines of investigation have suggested that estriol might be able to act in a complementary way with ER alpha-preferring estrogens to limit estrogen-induced cell proliferation and, possible, carcinogenesis."

- **Stegeman, B.H. et al. (2013). Different combined oral contraceptives and the risk of venous thrombosis: Systemic review and network meta-analysis. *British Medical Journal, 347,* f5298**

"Users of combined oral contraceptives with third generation progestogens have a higher risk of venous thrombosis than those using second generation progestogens. "

- **Dew, J.E. et al. (2003). A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric, 6,* 45-52.**

"A number of other small cohort and case-control studies have used HRT in women previously treated for breast cancer without adverse effect. None of these studies has shown an increased risk of recurrence."

"Low dose vaginal estrogens used (in this study) were estriol creams and pessaries in 36 (52%) and estradiol 25 mcg tablets in 33 (48%)."

"There was no evidence from this study to indicate any difference in the risk of recurrence of breast cancer for women using topical vaginal estrogen therapy compared with those who use no hormonal therapy."

"Limited systemic absorption has been reported with the use of vaginal estriol cream or suppositories, while marked systemic absorption can occur with Premarin cream. Endometrial proliferation has not been reported with vaginal estriol preparations."

- **Ellis, M.J. et al. (2009). Lower-dose vs. high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: A phase 2 randomized study. *JAMA, 302,* 774-780.**

"Women with advanced breast cancer and acquired resistance to aromatase inhibitors were given either 6mg or 30mg daily of Estradiol. Patients showed an improvement in their disease when given Estradiol, but the 6 mg dose was better tolerated and had less side effects.

"In conclusion, 6 mg of estradiol daily, which produces estradiol levels similar to those in ovulating premenopausal women, is an active low-cost treatment for postmenopausal women with advanced breast cancer and acquired resistance to aromatase inhibitor treatment and should be further investigated."

- **Fournier, A. et al. (2005). Breast Cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *International Journal of Cancer, 114*, 448-454.**

"The association between HRT use and breast cancer risk most likely varies according to the type of progestogen used. There was no or little increase in risk with estrogens used alone or combined with micronized progesterone."

"Our study confirms previous findings of an increase in invasive breast cancer risk with estrogens combined with synthetic progestins compared to no HRT use."

"Combinations containing micronized progesterone appeared to be associated with a significantly lower breast cancer risk than those containing synthetic progestins."

Progesterone Therapy

- **Burry, K.A. et al. (1999). Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *American Journal of Obstetrics and Gynecology, 180,* 1504-1511.**

Study looked at transdermal estradiol patch 0.5mg twice weekly and OTC progesterone cream 30mg q day for 2 wks. (started 2 days after the estradiol patch was applied) and then BID for 2 weeks.

"Even studies with low serum concentrations of progesterone have shown beneficial effects on the endometrium, suggesting a direct transit to the uterus for a "first uterine pass effect."

"Fanchin reported that 45 to 90mg vaginal progesterone gel induced normal secrectory transformation of the endometrium corresponding with plasma progesterone levels of 3.4 to 3.6 ng/ml."

"Thus it seems possible that the absorption of progesterone across mucus membranes, vaginal mucosa, and the skin may result in an increased bioavailable level of the hormone, therefore providing an endometrial effect with lower serum levels of progesterone."

"This study has demonstrated that progesterone is absorbed through the skin and that luteal levels of serum progesterone can be achieved."

- **Campagnoli, C. et al. (2005). Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *Journal of Steroid Biochemistry & Molecular Biology, 96,* 95-108.**

"The incidence of BC (breast cancer) is two-to-three times greater in women with serum levels of estradiol or testosterone in the higher quartiles or quintiles of the distribution."

"In this study, oral micronized progesterone, contrarily to synthetic progestins, did not increase BC risk in women treated with transdermal estradiol."

"A key metabolic alteration that increases BC risk is the resistance to insulin action on carbohydrates (insulin resistance: reduced insulin sensitivity), due to genetic and nutritional factors, with consequent hyperinsulinemia."

"High levels of free testosterone have been identified as a risk factor for BC both before and after menopause."
"Estrogens, particularly orally administered estrogens, are able to counteract metabolic factors that increase the risk of BC. One way they do this is by increasing insulin sensitivity and hence lowering circulating insulin levels."

"We therefore suggest that when HRT is indicated, preparations containing progesterone and not a synthetic progestin should be used, according to a sequential or cyclic-combined regimen. In this way the risk of endometrial cancer is minimized without increasing the risk of BC"

- **Holtorf, K. (2009). The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine, 121,* 1-13.**

"Four studies of patients using HRT, including either progesterone or MPA, compared efficacy, patient satisfaction, and quality of life. Women in all 4 studies reported greater satisfaction, fewer side effects, and improved quality of life when they were switched from synthetic progestins to progesterone replacement."

"Synthetic progestins have potential anti-apoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation. In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells. Progesterone also downregulates estrogen receptor-1 in the breast, induces breast cancer cell apoptosis, diminishes breast cell mitotic activity, and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1."

"Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens, potentially contributing to their carcinogenic effects, which are not apparent with progesterone."

"Use of unopposed postmenopausal estrogen from ages 50-60 years increased the risk for breast cancer to age 70 by 23 %."

"In contrast to the demonstrated increased risk for breast cancer with synthetic progestins, studies have consistently shown a decreased risk for breast cancer with progesterone."

"Melamend et al demonstrated that, when administered with estradiol, estriol may have a unique ability to protect breast tissue from excessive estrogen-mediated stimulation. Acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an antiestrogen."

"Synthetic progestins, in contrast (to progesterone), have completely opposite effect: they promote atherosclerotic plaque formation and prevent the plaque-inhibiting and lipid- lowering actions of estrogen."

"Transdermal estradiol, when given with or without oral progesterone, has no detrimental effects on coagulation and no observed increased risk for venous thromboembolism"

"Synthetic progestin can significantly increase insulin resistance, when compared with estrogen and progesterone."

- **Leonetti, H.B. et al. (2003). Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertility and Sterility, 79.***

This was a blinded study were participants were given daily 0.625mg of CEE and twice daily transdermal progesterone cream either 0%, 1.5 % or 4.0% for 28 days. An endometrial biopsy was performed after treatment. No increased risk of hyperplasia was found, and it was concluded that progesterone cream has an antiproliferative effect on the endometrium.

- **Skouby, S.O. & Jespersen, J. (2009). Progestins in HRT: Sufferance or desire? *Maturitas, 62,* 371-375.**

"There is mounting evidence that natural progesterone improves cardiovascular function in contrast to the synthetic progestin medroxyprogesterone acetate (MPA) used in the large scaled US investigations."

"Progesterone is rapidly cleared from the blood, which can present challenges regarding serum progesterone testing."

"Orally administered progesterone, even in micronized form, shows a wide variation of absorption and bioavailability in the individual person."

Relative binding affinities of progesterone and synthetic progestins to steroid receptors:

Oestrogen Therapy

- **Boothby, L.A. et al. (2004). Bioidentical hormone therapy: A review. *Menopause, 11*, 356-367.**

"Estrogen receptor alpha is mostly found I the endometrium, breast-cancer cell, and ovarian stroma cells, whereas estrogen receptor beta is mostly found in the kidney, intestinal mucosa, lung parenchyma, bone marrow, bone, brain, endothelial cells, and the prostate gland."

Binding affinities for estrogen receptor alpha and beta:

	Estrogen receptor Alpha	Estrogen receptor Beta
17-beta-estradiol	100	100
17-alpha-estradiol	58	11
Estriol	14	21
Estrone	60	37
4-OH-estradiol	13	7
2-OH-estrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16
Genistein	4	87
Coumestrol	20	140

"According to John Lee, MD. Normal salivary progesterone concentrations. . . can usually be obtained with topical doses of 15 mg per day."

- **Collaborative Group on Epidemiological Studies of Ovarian Cancer. (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *The Lancet* 385, 1835-1842.**

"Ecological studies have shown correlations between dramatic reductions in use of HRT in many countries, and declines in the rates of breast cancer in older women."

"Meta-analyses of data from the trials and observational studies show that the increase in breast cancer risk is greater for combined estrogen–progestin therapies compared with estrogen alone."

- **Laliberte, F. et al. (2011). Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause, 18,* 1052-1059.**

"After adjustment for confounding factors, ETS (transdermal) was associated with a statistically significant risk reduction for VTE and hospitalization-related VTE by 33% and 62%, respectively, compared with the oral estrogen-only HT cohort. Of note, the risk reduction associated with ETS was more pronounced for PE events."

"[These findings] are consistent with results from ESTHER, Renoux et al, and Cononico et al."

Thyroid

- **Aksoy, D.Y. et al. (2005). Effects of prophylactic thyroid hormone replacement in Euthyroid Hashimoto's Thyroiditis. *Endocrine Journal, 52,* 337-343.**

"Early treatment of euthyroid Hashimoto's thyroiditis patients with L-thyroxine may slow down not only the disease process itself but through its immune modulating events it may also affect the course of other auto-immune diseases which accompany."

- **Ma, S. G., et al. (2014). A novel treatment for subacute thyroiditis: administration of a mixture of lidocaine and dexamethasone using an insulin pen. *Mayo Clinic Proceedings*, 89, No. 6, 861-862.**

"Patients with subacute thyroiditis (SAT) generally have neck pain and fever. No fast-acting therapy has been reported. We hypothesized that intrathyroidal injection using an insulin pen filled with a mixture of lidocaine and dexamethasone could produce therapeutic benefit compared with oral medications"

"Insulin cartridges were filled with 3.0-mL mixtures that contained 50 mg of lidocaine, 3 mg of dexamethasone, and saline solution. The thyroid isthmus was injected with a 4-mm needle (32G) and the lobe with a 6-mm needle (32G) under ultrasound guidance."

"Most patients in the injection group reported rapid pain relief and significant neck relaxation within 1 week compared with the oral group (**P**<.0001). In addition, the frequency and duration of treatments were significantly less (**P**<.0001)."

- **Yamada, T. et al. (1978). An increase of plasma triiodothyronine and thyroxine after administration of dexamethasone to hypothyroid patients with Hashimoto's Thyroiditis. *Journal of Clinical Endocrinology and Metabolism,* 46, 784-790.**

Plasma T4 and T3 increased in all patients after administration of 2 mg dexamethasone for 4 weeks. The increase was greater in T3 than in T4.

Dexamethasone inhibits the peripheral conversion of T4 to T3, and also decreases TSH.

- **Mazer, N. et al. (2003). Transdermal testosterone for women: A new physiological approach for androgen therapy. *Obstetrical and Gynecological Survey,* 58, 489-500.**

Healthy women produce about 300mcg per day of testosterone.

"The 5 alpha reductase and aromatase activities present in the epidermal layer of nongenital skin (such as the abdomen) are relatively small, the degree of first-pass dermal metabolism of testosterone to dihydrotestosterone (DHT) and estradiol (E2) is likewise expected to be small when using a non-genital transdermal patch"

Giving testosterone orally can cause "marked reductions in the concentrations of SHBG and thyroxine-binding globulin, which may impact hormone bioavailability, and HDL cholesterol, which may adversely affect cardiovascular risk.

"The individual patient who requires both testosterone and ET, the use of transdermal E2 would result in a substantially greater increase in free testosterone levels than if oral estrogen therapy were given concomitantly with a testosterone matrix patch"

- **Miller, B. et al. (2000). Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause,* 7. 318-326.**

"The addition of androgens to HRT has been shown not only to improve sexual health but also to prevent bone loss. In fact, androgen receptors have been found in bone cells of both men and women. Whereas estrogen decreases bone resorption, androgens may promote bone deposition by increasing osteoblastic activity."

"The addition of methyl-testosterone to HRT in postmenopausal women has been reported to adversely affect lipid profiles, and may have hepatotoxic effects."

"The sublingual administration of micronized testosterone also avoids first passage through the liver, which may preclude the unfavorable lipoprotein effects.'

The study used either micronized estradiol 0.5mg or micronized estradiol 0.5mg plus micronized testosterone 1.25mg, and micronized progesterone 100mg if they had a uterus. This regimen was given BID.

"Micronized E2, P4, and T therapy increased BMD of both the lumbar spine and hip, whereas micronized D2 and P4 increased spinal BMD and maintained hip BMD."

"It has been suggested that progestogens may stimulate bone formation independent of estrogen. Although the synthetic nortestosterone-derived C19 progestins (i.e., noresthisterone) have been reported to have beneficial effects on bone density possibly because of their androgenic properties, the C21 progestins, MPA or P4 itself, have not consistently been shown to enhance bone metabolism."

"The results of this study indicate that besides relieving menopausal symptoms and restoring g therapeutic sex hormone levels, sublingually administered micronized E2, P4, and T successfully reduces metabolic bone markers of both resorption and formation, prevents bone loss, and results in significant increases in spine and hip BMD."

Androgen Therapy – DHEA

- **Labrie, F. (2010). DHEA after menopause: Sole source of sex steroids and potential sex steroid deficiency treatment. *Menopause Management*, 19, 14-24.**

"Postmenopausal women suffering from vaginal atrophy received daily DHEA or placebo intravaginally for 3 months. A rapid and very marked improvement of all the symptoms and signs of vaginal atrophy was observed, with no change in circulating estradiol or testosterone."

"Other clinical data suggests that DHEA could also exert beneficial effects on bone and muscle loss, skin atrophy, adiposity and type 2 diabetes."

"This marked reduction in the secretion of DHEA by the adrenals during aging results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues, a situation believed to be associated with a series of medical problems of menopause: insulin resistance, fat accumulation, bone loss, muscle loss, type 2 diabetes, vaginal atrophy and skin atrophy, memory and cognition loss, and possibly Alzheimer's disease."

"These actions also indicate a unique activity of DHEA on bone (namely, a stimulation of bone formation) while ET, HT, bisphosphonates, selective estrogen-receptor modulators and calcitonin only reduce the rate of bone loss."
"Compared to placebo, DHEA produced a 68% improvement in the ASF arousal/sensation domain, a 39% improvement in the arousal/ lubrication domain, a 75% improvement in orgasm, and a 57% improvement in dryness during intercourse."

"There is no reason to believe that the metabolism, action and safety of exogenous DHEA given at physiologic doses to symptomatic women would be different from the metabolism and action of endogenous DHEA in women who have sufficient levels of DHEA to remain free from the symptoms of menopause."

"This is well supported by the absence of DHEA-related safety issues in the medical literature, in which high doses of DHEA have been used orally or percutaneously in a large series of women for up to 2 years."

- **Labrie, F. et al. (2007). Metabolism of DHEA in postmenopausal women following percutaneous administration. *The Journal of Steroid Biochemistry & Molecular Biology*. 103, 178-188.**

"Following cessation of estrogen secretion by the ovaries in postmenopausal women, all estrogens and almost all androgens are made locally from DHEA in the peripheral target tissues with minimal diffusion of the active steroids outside these tissues."

Subjects were given 3ml twice daily of one of the 5 concentrations: Placebo, 0.1% DHEA, 0.3% DHEA, 1% DHEA, and 2% DHEA for 13 weeks.

"It is quite clear from the present data that DHEA is preferentially transformed into androgens rather than into estrogens in postmenopausal women."

- **Labrie, F. et al. (2009). Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause,* 16, 923-931.**

This was more data from the above study looking specifically at sexual function.

"The present data show . . . that local intravaginal treatment with DHEA. . . causes a marked improvement for all four aspects of women's sexual dysfunction, namely, desire/ interest, arousal, orgasm, and pain at sexual activity."

"In postmenopausal women with normal adrenal function, and increase in sexual excitation and libido was reported at 6 months of DHEA administration."

- **Labrie, F. DHEA, important source of sex steroids in men and even more in women. Chapter 4. In *Progress in Brain Research,* 182, 97-148.**

"No serious adverse event related to DHEA has ever been reported in the world literature (thousands of subjects exposed) or in the monitoring of adverse events by the FDA (millions of subjects exposed) thus indicating, as expected from its known physiology, the excellent safety profile of DHEA."

The author listed 50 separate studies using DHEA doses from 25mg up to 700mg orally and did not report any negative effects.

"The androgens testosterone and DHT as well as E2 made in peripheral tissues from DHEA of adrenal origin exert their action locally in the same cells where their synthesis takes place. This sophisticated mechanism permits to maintain biologically active levels of intracellular estrogens and/ or androgens in specific tissues in need of these sex steroids while the same steroids leak in the blood at very low levels, thus sparing the other tissues from a potentially negative influence."

"When DHEA was analyzed from 17 different (OTC) formulations, 3 formulations contained no detectable DHEA while most tablets/ capsules had 59-82% of the amount indicated on the label while one tablet had 149% of the amount of DHEA stated."

"In the human, data indicate that DHEA inhibits atherosclerosis, reduces cardiovascular risk markers, and improves endothelial function."

"It has been found that women who underwent bilateral oophorectomy before age 45 experienced an increased mortality associated with CVD compared with referent women."

- **Slayden, S. M. et al. (1998). The Effect of 17B-Estradiol on adrenocortical sensitivity, responsiveness, and steroidogenesis in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism, 83*, 519- 524.**

"Adrenopause may in part be responsible for the increasing incidence of cardiovascular disease, glucose intolerance, cancer, and the decline in bone mass and immune competence with age."

"It is unlikely that the hypoestrogenism of menopause contributes to the decline in AAs noted with age. Furthermore, menopausal estrogen replacement, at least in physiological amounts administered transdermally, cannot be expected to reverse the suppressed production of these androgens."

- **Edwards, L. et al. (2011). Hypocortisolism: An evidence-based review. Integrative Medicine, 10, 26-33.**

"Many clinical syndromes, including "burn out, " fibromyalgia (FMS), posttraumatic stress disorder (PTSD), autoimmunity, allergies, inflammation, and chronic pelvic pain, have been associated with HPA axis dysfunction and hypocortisolism"

"When chronically elevated, cortisol has potent metabolic effects as a catabolic hormone in all organs and tissues except the liver. Systemic effects of elevated glucocorticoids include increased gastric acid secretion, decreased collagen production, reduced diuresis, reduced bone formation, hyperglycemia, and hippocampal neuronal damage. Cortisol also impairs thyroid hormone production and function and causes numerous aberrations in immune system regulation and function."

Theories on Pathophysiological Evolution of Hypocortisolism:

1. Developmental

   "After an initial period of HPA axis hyperactivity and cortisol hyper-secretion, hypocortisolism may ultimately develop as a type of maladaptive "overcompensation" of the self-preservation mechanisms designed to protect the metabolic machinery (in particular the brain) from the effects of persistent cortisol elevation."

2. CRF Down regulation

   "An increase in the sensitivity of the HPA axis to cortisol during periods of excessive glucocorticoid production induces negative feedback control on further release of stimulating hormones, thereby resulting in hypocortisolism"

3. Inadequate Glucocorticoid Signaling

   "Decreased glucocorticoid bioavailability accounts for one possible mechanism and may develop secondary to decreased adrenal cortisol production, alterations in cortisol binding protein levels, enzymatic conversion of cortisol to other hormones, or action of the "multidrug resistant pump, " which potentiates cortisol exit from the cell."

4. Intrinsic Adrenal Gland dysfunction

   "In the face of adrenocortical atrophy, glucocorticoid production would diminish and compensatory glucocorticoid receptor up regulation does not occur.

5. Adaptive Response

   "Hypocortisolism may occur as an adaptive survival mechanism to promote a more vigorous immune response."

   "Breast Cancer patients who demonstrate significant post-treatment exhaustion have been shown to have significantly altered HPA axis activity in combination with elevated IL-6 levels and flattened cortisol curves with an apparent consequential increase in mortality and metastasis."

   "Diseases such as obesity, increased coronary artery calcification, and metabolic syndrome have been linked to circadian abnormalities in cortisol, particularly flattened cortisol curves."

Appendix D: Australian Compliance Policy Guide on Compounded Medications

Australian medicine manufacturers must hold a manufacturing licence issued by the Therapeutic Goods Administration (TGA). This license requires that the manufacturer comply with the Code of Good Manufacturing Practice (cGMP). According to the *Therapeutic Goods Regulations of 1990* (Pharmacy Board of Australia, 2015) compounded products are exempt from registration with the TGA if they "are dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person" and they are prepared in a pharmacy "for supply (other than by wholesale) on or from those premises". Pending these conditions, extemporaneously dispensed medicines:

(i) are not subject to evaluation by the TGA and therefor do not appear on the Australian Register of Therapeutic Goods (ARTG);
(ii) do not need to be prepared in facilities which comply with the cGMP.

In Australia, compounding is defined as the extemporaneous preparation and supply of a single 'unit of issue' of a therapeutic product intended for immediate use by a specific person in response to an identified need. A compounded medicine may be prepared only in circumstances where:

- an appropriate commercial product is unavailable;
- a commercial product is unsuitable (e.g., if a patient experienced an allergy to an excipient in the commercial product); or
- when undertaking research sanctioned by a recognised human research ethics committee.

It is the pharmacist's responsibility to:

- conduct a risk assessment of the safety and the suitability of the compounding facilities, equipment, devices, training and proposed compounded operations
- risks assessment of the suitability of the compounding formulation for the specific patient considering evidence of efficacy, stability and safety
- ensure that the preparation has been compounded in accordance with pharmacopoeial formulations when available, and in a manner which ensures quality, safety, and efficacy;
- conduct environmental monitoring of facility: temperature, humidity, pressure, light
- ensure all staff are appropriately trained, competency standards are maintained
- ensure that SOPs are documented, followed and the compounding procedure has been documented
- use pharmacopoeial grade APIs from TGA-registered facilities
- assign expiry dates according to pharmacopoeial formulas or APF or evidence based on stability indicating assays
- ensure all packaging and labelling of the compounded preparation is appropriate;
- approve the supply of the medicine to the consumer, whether a prescription medicine or over the counter medicine
- have a functional system for recalls, complaints and corrective and preventative action
- counsel the patient and ensure that the patient is provided relevant information about the compounded preparation in relation to use, adverse events, storage, expiration and disposal

The compounding of products where no precedents in reputable references exist must be justified through the pharmacist obtaining additional data and/or evidence. If deciding to compound such products, a pharmacist should document:

- evidence of appropriateness of the intended formulation that is accessible for all future compounding of this formulation and which includes:
  - efficacy, pharmacokinetic data, clinical data, and the basis for the assigned expiry date of the intended formulation;
  - the process to maintain the safety of the pharmacy staff where the compounding is taking place.

- any other steps which ensure that the dispensing and supply of the compounded medicine is consistent with the safety of the individual patient.

In the absence of such documented evidence, pharmacists must not compound such products.

When the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Therapeutic Goods Act, regulators will seriously consider enforcement actions.

In determining whether to initiate such an action, regulators will consider whether the pharmacy engages in any of the following acts:

- Batch production by compounding pharmacies for unknown patients without cGMP compliance and ARTG listing.
- Compounding of drugs in anticipation of receiving prescriptions.
- Compounding drugs that were withdrawn or removed from the market for safety or efficacy reasons.
- Compounding finished drugs from bulk active ingredients that are prohibited
- Compounding investigational drugs for clinical trials without the approval of a sanctioned ethics committee.
- Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been manufactured in a TGA-registered facility.
- Receiving, storing, using drug components not guaranteed or determined to meet official compendia requirements.
- Using commercial scale manufacturing or testing equipment for compounding drug products.
- Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale, without having a manufacturing licence.
- Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available TGA-approved drug products.
- Failing to operate in conformance with applicable laws, regulations and guidelines such as Pharmacy Board, State/Territory laws, Federal laws, relating to the practice of Pharmacy, including:
  Guidelines on dispensing of medicines (Pharmacy Board of Australia)
  Guidelines on compounding of medicines (Pharmacy Board of Australia)
  Therapeutic Goods Act (1989)
  Therapeutic Goods Regs (1990)
  Professional Practice Standards 2017 v5, The Pharmaceutical Society of Australia (PSA). Standard 5 applies to both Simple and Complex compounding of non-sterile and sterile compounding preparations
  *Australian Pharmaceutical Formulary and Handbook, (*APF) ed 23, The Pharmaceutical Society of Australia
  QCPP: Australian Standard S 85000:2011, Pharmacy Guild of Australia - the Quality Care Pharmacy Standard, a quality management system for QCPP accreditation
  SHPA Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments, The Society of Hospital Pharmacists of Australia.
  Occupational, health and safety standards
- Compounding pharmacies making therapeutic claims and other breaches of the Therapeutic Goods Advertising Code.

The foregoing list of factors is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case. Other guidance documents interpret and clarify regulators' positions concerning nuclear pharmacy, hospital pharmacy, mail order pharmacy, and the manipulation of approved drug products.