

Module 8 – Reproductive conditions

Learning objectives:

At the end of this module you should be able to:

1. Understand the impact of gastrointestinal conditions on fertility
2. Describe how endometriosis impacts fertility
3. Explain the impact of insulin resistance on fertility
4. Comprehend how thyroid conditions influence fertility

Before a couple conceives it is recommended that they optimise any pre-existing dietary conditions which may have an impact on the epigenetic coding of the foetus, or the nutritional status and/or fertility of the couple. If the couple is experiencing unexplained infertility, testing for the following conditions may also be considered.

Gastrointestinal conditions

Coeliac Disease

Research tells us that women with undiagnosed Coeliac Disease have an 8.9 fold increased risk of multiple spontaneous abortions, compared with either those women who don't have Coeliac Disease, or those women who have got well treated Coeliac Disease.¹ In fact, the NICE guidelines recommend undertaking Coeliac serology in people with unexplained subfertility or who are experiencing recurrent miscarriages.²

Important considerations for clients with Coeliac Disease include ensuring that they are adhering to a strict gluten free diet, monitoring at risk nutrients including iron, vitamin D, vitamin K, vitamin B6, folate and iodine, and screening for other autoimmune conditions (such as diabetes and thyroid diseases). It's salient to note that unlike commercial bread, many gluten free breads aren't fortified with nutrients such as folate and iodine. If possible, it is preferable to focus on optimising nutrition with adequate time to rectify any malabsorption issues.

Inflammatory Bowel Disease

The chances of pregnancy with Inflammatory Bowel Disease (IBD) are very similar to women who don't have it if the IBD is well treated and in remission. An acute flare up episode of IBD, a significant loss of body weight and/or nutritional deficiencies can all impact fertility. Unfortunately, active IBD at the time of conception can result in acute IBD throughout pregnancy, so if possible, it is recommended that conception wait until IBD is in remission. Abdominal or pelvic surgery (partial or total colectomy) can also decrease fertility rates, most likely due to internal scarring around the fallopian tubes. There are also instances where the medications used to treat IBD can cause a temporary, but usually reversible reduction in fertility too.³

Research shows an increased risk of pregnancy complications such as miscarriage and preterm delivery when IBD flares up during pregnancy, so it's important to ensure that clients with IBD are

well educated on dietary modifications for minimising flare ups, prior to becoming pregnant.⁴ Corticosteroid medications used to treat IBD flare ups, have been associated with a small, but significant risk of Neural Tube Defects, so it is recommended that women with IBD who are trying to conceive take a 5mg folic acid supplement for at least 1 month prior to conception. Iron and vitamin B12 are common nutritional deficiencies in clients with BD, however, high doses iron supplements can aggravate an IBD flare up, so aim to increase it slowly prior to conception if possible. Selenium, magnesium, zinc and some Vitamin D are additional common deficiencies in clients with IBD, so check biochemistry and replace as required.⁵

Endometriosis

Endometriosis is a chronic inflammatory disorder of the reproductive organs which affects over 10% of women at some point in their life.⁶ The condition results in tissue, which is similar to the lining of the uterus, growing in other parts of the body, most commonly within the pelvis. The stimulus for this tissue growth is the female hormone oestrogen. Currently, there is no known cure. Symptoms include severe menstrual pain and bleeding, chronic pelvic pain and sub-fertility. There are four stages of endometriosis:

Stages of Endometriosis	
Peritoneal endometriosis: Stage I (1-5 points)	Minimal Few superficial implants to the peritoneum
Ovarian endometriomas: Stage II (6-15 points)	Mild More and deeper implants Dark, fluid-filled cysts (also known as 'chocolate cysts') start appearing within the pelvis (most commonly in the ovaries)
Deep infiltrating endometriosis I: Stage III (16-40 points)	Moderate Many deep implants Small cysts on one or both ovaries Presence of filmy adhesions
Deep infiltrating endometriosis II: Stage IV (>40 points)	Severe Many deep implants Large cysts on one or both ovaries Many dense adhesions

Table 1. Stages of endometriosis. Adapted from ASRM ⁷

Endometriosis and Infertility

According to research between 30% and 50% of women with endometriosis are infertile.⁸ The association between endometriosis and infertility is well supported throughout the literature, but a definite cause-effect relationship is still debated. The primary causes however are related to both egg health and anatomical changes including (but not limited to) scarring, damage and/or blockage of the fallopian tubes and ovaries. The scarring/blockage caused by the endometrial cells may interfere with ovulation and/or can prevent the journey of an egg along the fallopian tube and/or the sperm from reaching the egg.

Possible causes for reduced fertility in women with endometriosis

- Adhesions
- Chronic intraperitoneal inflammation
- Disturbed folliculogenesis caused by pituitary dysfunction resulting in reduced oocyte quality
- Luteinized unruptured follicle
- Luteal phase defects (ovaries don't secrete adequate progesterone, so endometrium doesn't adequately thicken)
- Progesterone resistance (which results in the growth of endometriotic tissue and increased inflammation)
- Detrimental effects on spermatozoa
- Anti-endometrial antibodies
- Dysfunctional uterotubal motility

Table 2: Possible causes for reduced fertility in women with endometriosis. Adapted from Tanbo and Fedorcsak (2017) ⁹

Laparoscopic surgery may be undertaken to remove endometriotic patches, adhesions, implants, cysts and nodules either to improve fertility or simply to reduce symptoms.¹⁰ If this procedure is unsuccessful, IVF treatments may need to be considered.

Endometriosis and Dietary Management

Altering diet may help in reducing symptoms and optimising fertility.¹¹ As endometriosis is an inflammatory disorder, recommendations include consuming foods which can reduce inflammation within the body and foods which also influence oestrogen levels.¹²

Dietary factors that may decrease the risk of endometriosis include:

- consumption of vegetables,
- antioxidant vitamins,
- B-group vitamins,
- dairy products rich in calcium and vitamin D,
- fish oils, and
- Omega-3 fatty acids.

The dietary factors that may potentially increase the risk of developing endometriosis include:

- consumption of trans unsaturated fatty acids,
- red meat and ham, and
- alcohol.

Level of evidence II and III (retrospective studies).¹³

Currently, there are no clear correlations between particular food products and the risk of endometriosis. Further research is needed in order to fully understand the influence of consumed food products on the risk of development of this disease.

Fats

Trans fats and refined oils induce an inflammatory response in the body. Palmitic acid has also been linked to increased rates of endometriosis.¹⁴ This fat is found mostly in red meat and again heightens the inflammatory response in the body.

Omega-6 is a major pro-inflammatory factor in the body. Conversely, the anti-inflammatory effect of omega-3 fatty acids have been shown to reduce the effects of endometriosis, even with short-term diet change.¹⁴ Furthermore, reducing saturated fat by 50% has been found to reduce oestrogen levels by 20%.¹⁵

Antioxidants

Women with endometriosis have an increased number of highly reactive substances in their body (free radicals). Free radicals increase 'oxidative stress'. Antioxidants can reduce the number of free radicals by binding with them to create a more stable form. This reduces the amount of oxidative stress and therefore reduces inflammation in those with endometriosis. One study researched the effects of antioxidant supplementation (vitamins E and C) on endometriosis pain and found that 43% of those with higher intake of antioxidants reported less pain compared to 0% in the group without supplementation.¹⁶ Not only this, but three inflammatory markers (substances produced by/ associated with inflammation) were found to be significantly lower in those taking the antioxidant supplement compared to those without supplementation. Therefore, it was concluded that increasing antioxidant intake in women with endometriosis had a positive effect on their condition.

Fibre

Fibre can help excrete oestrogen out of the body through a process known as 'barrier protection' in which fibre surrounds substances and takes them on a journey to outside the body before they can be absorbed. Excess oestrogen in the body can worsen the effects of endometriosis by promoting inflammation.¹² Too much oestrogen stimulates the formation of lipid substances which act like hormones – these are called prostaglandins. These increase inflammation and heighten the pain in pelvic regions of those with endometriosis. Along with this, oestrogen has been found to actually increase endometriosis cell growth and numbers, meaning larger cells and more of them. Not all fibres are created equally, however.¹¹ High GI fibres increase the insulin response which may lead to it increasing the numbers of endometriosis cells.

Fruit and Vegetables

There is a strong inverse relationship between fruit and vegetable consumption and endometriosis in most research due to these combining factors. A study by Britton and colleagues in 2003 found that women who had a high intake of fruit and vegetables were less likely to have endometriosis.¹⁷ Brassica vegetables in particular have been found to reduce estrogen levels.¹⁸

However, it's worth noting that exposure to pesticides and dioxins found on fruit and vegetables have been positively associated with endometriosis and its symptoms.¹² This may be due to certain pesticides interfering with hormonal pathways and contributing to oxidative stress. It has even been found that fruit consumption can actually worsen the symptoms for women with endometriosis, most likely due to higher levels of pesticide residue and dioxins being found on some fruits.¹⁹

Adenomyosis

Endometriosis is where endometrial cells grow outside the uterus. Adenomyosis is a condition whereby endometrial cells grow inside the uterine wall.²⁰ Adenomyosis is also a common cause of

subfertility.²¹ Compared to endometriosis, women with adenomyosis are more likely to be overweight or obese (potentially as they are often diagnosed at a later age?) and exposed to increased endogenous estrogen (such as the oral contraceptive pill or Hormone Replacement Therapy).²² A 2017 study of 300 women with adenomyosis found that 42.3% of these women also had endometriosis.²³ Initial research into adenomyosis suggests that the same dietary recommendations for endometriosis should be made.

Insulin resistance

Insulin resistance is another common cause of subfertility. Women who have insulin resistance find excess body fat forms a barrier to insulin trying to get through to the bloodstream, rather like a condom to sperm, so that it can't get through and work effectively. In turn, hyperinsulinemia leads to carbohydrate cravings, inflammation, oxidative stress and more weight gain.²⁴ The excess body fat will then produce higher levels of estrogen, resulting in an increasing spiral of excess insulin production and excess fat deposition, followed by excess estrogen production.²⁵

A 2012 study looking at the prevalence of metabolic syndrome and insulin resistance in overweight and obese women measured that 70.6% of those women were insulin resistant.²⁶ Furthermore, many people go undiagnosed until complications such as infertility arise.

A landmark study by Brothers, J.K. et al. undertaken in 2010 on mice found that the pituitary gland responds to chronically high levels of insulin by triggering a cascade of hormonal changes which impair fertility.²⁷ Lean mice had six times more successful pregnancies than obese mice. Obese mice which had their pituitary-insulin receptors removed had five times more successful pregnancies than obese mice with their pituitary-insulin receptors intact. In addition to affecting estrogen levels, insulin resistance also impacts the production of progesterone and luteinising hormone, further altering the hormonal environment of the ovaries and impacting fertility.²⁸

PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Estimated prevalence is 12 to 18%, with higher rates in at risk groups, such as the Indigenous (up to 21%).²⁹ PCOS is a complex condition characterised by hyperandrogenism, ovulatory dysfunction, increased risks for endometrial hyperplasia, diabetes and cardiovascular disease.

PCOS and Infertility

PCOS is associated with increased fertility difficulties due largely to ovulatory dysfunction, poorer quality endometrial lining and increased risk of miscarriage.³⁰ As insulin resistance is a key contributor to the pathogenesis of the syndrome, dietary changes can significantly see a reduction in infertility rates.³¹

PCOS and dietary management

Research suggests that a relatively low reduction in weight (over 5%) is adequate to improve insulin resistance, reproductive system dysfunction and fertility in overweight women with PCOS.³² In the PCOS population, there is a high percentage who are overweight, but Barr et al (2013) highlighted many women with PCOS are considered lean and thus weight management strategies are not appropriate.³³ Sorensen et al (2012) commented "lean and overweight women with PCOS are more insulin resistant than are healthy women with similar BMIs".³⁴

The following two studies focus on how to optimise insulin resistance in women with PCOS, but both agree there is a lot more research to be done in this area.

In the first study: a nonrandomised group of 26 participants were tracked over a 36-week period. It included a habitual diet control phase (0-12 weeks); a low GI dietary intervention phase (12 to 24 weeks) and a follow up phase (24 to 36 weeks).³³ Results were that a low GI diet in women with PCOS did improve insulin sensitivity without weight loss occurring. Limitations to the study was its population size and that participants simultaneously reduced their saturated fatty acid (SFA) intake during the intervention phase, despite not being given advice to do so. This reduction in SFA intake could have affected insulin sensitivity.

In the second study, the objective was to compare the effects of high protein (HP) diets to standard protein (SP) diets on concentrations of total and free testosterone.³⁴ The second objective was to investigate effects on glucose metabolism, lipid profile, body weight and composition in women with PCOS. The 6-month trial had a 53% drop out rate, resulting in a small final study group (n=27). The authors commented this would have had consequent reduction in power to detect changes. The key findings were:

- Greater weight loss occurred in the HP group (n=14; total loss of 7.7kg; SP n=13; total loss of 3.3kg) but this may have been due to more support given to participants and clients liked having something more to focus on.
- There were no consistent effects on total and free testosterone concentrations.
- The HP diet did have a positive influence on glucose metabolism independent of weight loss.
- There was no difference in blood lipids between the groups.

More research is needed in how to change insulin resistance in PCOS women regardless of weight; especially if improving insulin resistance is a key factor to improving the progression of the disorder and increasing fertility rates for women with PCOS.

A systematic review on all published articles up to 2012, was conducted by the Adelaide University.³⁵ A total of 4,154 articles were retrieved, and the summary findings were:

- A monounsaturated fat-enriched diet was associated with greater weight loss;
- A low-glycemic index diet was associated with improved menstrual regularity;
- A high-carbohydrate diet was associated with an increased Free Androgen Index;
- Both a low-carbohydrate or low-glycemic index diet were associated with reductions in insulin resistance, fibrinogen, total, and high-density lipoprotein cholesterol;
- A low-glycemic index diet was associated with improved quality of life, and
- A high-protein diet was associated with improved depression and self-esteem.

Microbiome

Recent research has been investigating a relationship between the gut microbiome and PCOS and suggests that women with PCOS tend to exhibit reduced biodiversity in the gut microbiome.³⁶ Particularly, hyperandrogenism, total testosterone levels and hirsutism were correlated with lower biodiversity in the gut microbiome.

Nutritional supplements

Links between vitamin D and infertility in woman with diagnosed PCOS is being investigated.³⁷ Two large clinical trials have been analysed, revealing vitamin D deficiency was associated with a reduced likelihood of these women becoming pregnant and delivering babies if PCOS was the underlying cause of infertility. The authors note that perhaps the most significant finding is that vitamin D deficiency seemed to be particularly important for women with PCOS. Inositols have also been found

to be effective for women with PCOS, improving metabolic and hormonal state and restoring spontaneous ovulation.³⁸

Thyroid conditions

Thyroid diseases are common in women of child-bearing age, so it is essential to review your patient's thyroid function.³⁹

Thyroid conditions and fertility

Most thyroid conditions are caused by autoimmunity. These conditions have a genetic link. Babies born with a family history of thyroid conditions have a higher risk of also having a thyroid condition and other autoimmune conditions.⁴⁰

Secondly, thyroid hormones interact with reproductive hormones, including estrogens and progesterone, to preserve normal function of the ovaries and maturation of the oocyte.⁴¹ If the thyroid gland releases too much (hyperthyroidism) or too little (hypothyroidism) thyroid hormones, the balance of reproductive hormones can be impaired with consecutive thyroid-related fertility problems such as ovulation disorders, irregular periods, and trouble getting pregnant or carrying a baby to term. Experts in the field recommend that the TSH concentration, should ideally be kept in the lower half of the reference range before pregnancy as this has been associated with a lower risk of miscarriage.

Thirdly, requirements for thyroid hormones, especially T4 significantly increase during pregnancy to assist with neurological development of the foetus, so the reference ranges for thyroid hormones change during pregnancy.⁴² Untreated thyroid conditions may result in cognitive impairment of the foetus.

Thyroid conditions and diet

Nutritional considerations for clients trying to conceive who have thyroid issues include:

Iodine

Many fertility and prenatal supplements now contain iodine. The reason for this is because iodine composes an important part of thyroid hormones.

The thyroid gland produces two primary hormones - thyroxine (also referred to as T4) and tri-iodothyronine (also referred to as T3). The numbers 3 and 4 refer to the number of atoms of iodine in the hormones. Iodine is essential for the production of thyroid hormones and women need about 150 micrograms each day (increasing to 220mcg per day during pregnancy). Iodine is found in a wide range of nutritious foods as it comes from the soil and sea. Seafood and fish is one of the best sources of iodine, so if your patient is meeting the recommended requirements of two to three serves of fish per week, plenty of fresh fruit and vegetables, some wholegrains and 3 serves dairy per day, then she'll most likely be meeting her iodine requirements. However, we know that this is rare, and instead, most women consume a high intake of processed foods which are low in micronutrients, including iodine. But please note, that iodine supplements can be dangerous for women who have Grave's disease.

Goitrogens

Goitrins can interfere with the synthesis of thyroid hormones, although this usually only occurs when coupled with an iodine deficiency. Goitrins are found in cruciferous vegetables, like broccoli,

cauliflower and cabbage, soy and millet, which is most commonly consumed in large quantities by those following a gluten free diet.

Research has found that people who take excessive amounts of soy products, usually via supplements, are more likely to have hyperthyroidism.⁴³ Furthermore, there is some suggestion that people who have hypothyroidism and are taking thyroxine medications should avoid taking large amounts of soy. Please note that this doesn't mean that they need to avoid soy foods altogether. It's safe to have one or two serves of soy foods, like tofu, soy milk or faux meat each day, but advised not to be consumed at the same time as thyroid medications (a two-hour gap should be sufficient in most cases). Soy capsules should be avoided.

It is also important to note that the goitrogenic effect of cruciferous vegetables is erased when they are boiled, so don't let this be an excuse for your clients not to eat their broccoli! ⁴⁴

Nutritional supplements

Nutritional supplements, particularly calcium, iron and chromium can impair the body's ability to absorb levothyroxine, it is recommended that they be taken at least four hours apart.⁴⁵ As many clients will be taking fertility supplements it is essential to check the timing of their ingestion.

Vitamin D

Vitamin D deficiency is common, and it is even more common in people with hypothyroidism. In fact, one study found that 90% of people with hypothyroidism had a vitamin D deficiency.⁴⁶ Researchers aren't yet clear if vitamin D deficiency increases the risk of hypothyroidism, or hypothyroidism increases the risk of vitamin D deficiency, but either way, if your client has hypothyroidism, it's worth reviewing their vitamin D levels prior to conception.

Vitamin D is also important for women with hyperthyroidism, as hyperthyroidism, particularly Grave's disease has been found to cause bone loss, and obviously, vitamin D is essential for healthy bones.⁴⁷

Selenium

The highest concentration of selenium is found in the thyroid gland, and it has been shown to be a necessary component of enzymes integral to thyroid function. Selenium is an essential trace mineral and has been shown to have a profound effect on fertility in both men and women.

A meta-analysis of randomized, placebo-controlled studies has shown benefits of selenium on thyroid antibodies in people with Hashimoto's, but this effect seems more pronounced in people with a selenium deficiency or insufficiency at the outset.⁴⁸ Conversely, an excessive intake of selenium can cause gastrointestinal distress, so clients with Hashimoto's may benefit from having their selenium levels tested and incorporating healthful, selenium-rich foods in to their diets, such as Brazil nuts, tuna, crab, and lobster.

Metabolism

Hypothyroidism can make it difficult to lose weight as it slows down the body's metabolic rate.⁴⁹ Aim to prevent further weight gain by modifying kilojoule intake, increasing energy expenditure and liaising with the client's medical team about their thyroid function.

Exercise elevates the effectiveness of levothyroxine in the bloodstream by approximately 30%, so exercising is an excellent way to achieve and maintain weight loss for someone with hypothyroidism.



Women with hyperthyroidism can lose weight rapidly secondary to a high metabolism. This can result in muscle catabolism, which can lead to future weight issues. Assist clients with hyperthyroidism to stabilise their weight by increasing caloric intake until their hormones have stabilised.

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