

# Module 5 – Implantation

## Learning objectives:

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

1. Grasp how the 'implantation rate' is calculated
2. Understand how 'recurrent implantation failure' is defined
3. List the common dietary-related factors that can impact 'recurrent implantation failure' and understand how dietary modification may optimise implantation rates
4. Have an awareness of key nutrients that are associated with improving implantation rates
5. Identify recommended dietary considerations for recurrent miscarriages

## Optimising implantation

Now, let's go back to sex education 101. After the egg is fertilised by the sperm in the fallopian tube, it continues to travel down the fallopian tube and implants itself in the lining of the uterus.

Alternatively, for a woman who is undergoing IVF, a fresh or frozen 'transfer' occurs and then the woman undergoes the dreaded 'two week wait' to see whether the blastocyst implants or not. If human chorionic gonadotropin (hCG) levels surge, then the embryo has implanted and the Mumma is pregnant. Well, at this stage (prior to 5 weeks gestation), it is known colloquially as a 'chemical pregnancy' due to the fact that this early in a pregnancy, women have no way of knowing that they are pregnant other than through biochemical tests... the baby is too small to be seen on an ultrasound and many women may not have even recognised that they had skipped a period.

The 'implantation rate' is the percentage of embryos which successfully undergo implantation compared to the number of embryos transferred in a given period. As an example, in 2017 the Cleveland Clinic reported an implantation rate of nearly 60% at a maternal age of less than 35 years, 40% at 35 to 37 years, 30% at 38 to 40 years, and 18% at 41 to 42 years.<sup>1</sup> These percentages increased with preimplantation genetic screening.

## Recurrent implantation failure

Recurrent implantation failure (RIF) refers to cases in which women have had three failed IVF attempts with good quality embryos.<sup>2</sup> However, it is essential to take advanced maternal age and embryo stage into consideration. The failure of embryo implantation can be a consequence of the health of uterus or the health of the embryo. We've previously discussed the health of the egg and sperm (and thus the embryo), so we're now going to consider uterine health.



### Anatomical abnormalities

Fibroids are non-cancerous lumps of tissue found in the uterus. They are very common, and usually don't cause any problems, but if they're in the wrong spot, they can cause implantation failure. The following have been linked to uterine fibroid risk:

**Alcohol** – women who drink alcohol seem to be more likely to have fibroids than those who don't.<sup>3</sup> This is believed to be because women who drink alcohol tend to produce excess estrogen hormones.<sup>4</sup>

**Caffeine** - High intakes of caffeine, over 500 milligrams per day have also been found to impact hormone levels which may cause fibroid production.<sup>5</sup>

**Fruits and vegetables** - studies suggest that fruit and veg are one of the best foods to eat when it comes to reducing the risk of fibroids. Current studies seem to suggest the need for at least two servings per day of fruit and four servings per day of veg.<sup>6</sup> Fruits and veg high in vitamin A seem to be particularly beneficial.

**Dairy products** - Studies suggest that a higher intake of dairy foods is protective against uterine fibroids.<sup>7</sup> At the moment there is no conclusive research on why, but theories include their high calcium content, or another compound called butyric acid which is commonly found in dairy. The research doesn't show any difference between high fat or low-fat dairy.

**Red meat and ham** - Studies suggest that women who consume more of these foods are more likely to develop fibroids.<sup>8</sup>

**Unsaturated fats** - monounsaturated and polyunsaturated fats appear to be protective against uterine fibroids, whereas saturated fats are associated with an increased risk.<sup>9</sup> The higher levels of saturated fat in red meat and ham may explain why these foods are linked to an increased risk of fibroids.

**Food additives** - Research suggests that women who have a higher intake of food additives such as colours, artificial flavours and preservatives, have a higher risk of developing uterine fibroids than those who consume more whole foods.<sup>10 11</sup>

**Bisphenol A** - Emerging research suggests that Bisphenol A (BPA) found in plastic may be one of the main reasons why rates of fibroids have been on the rise.<sup>12</sup>

**Excess calorie intake** - high levels of body fat resulting in hyperestrogenism is believed to be one of the main causes of uterine fibroids.<sup>13</sup>

### Thin Endometrium

The uterus is a dynamic organ that is subjected to cyclic restructuring during the menstrual cycle and undergoes enormous transformations during pregnancy. One of these transformations, termed decidualization, is the transformation of the endometrial lining of the uterus into secretory and hypertrophic/rounded cells to establish a microenvironment favorable for pregnancy and to provide physical support for placental attachment. Having a thin endometrium minimises chances of implantation. Medical techniques are the primary treatment for thickening the endometrium, although there is some suggestion that nutrition may have an impact. There are some suggestions



that vitamin E supplementation may assist.<sup>14</sup> L-arginine is another supplement that is commonly used and has a small amount of research supporting its use.<sup>15 16 17</sup>

One interesting study found that women who had a higher intake of wholegrains had a greater chance of implantation.<sup>18</sup>

### Endometritis

Endometritis is an inflammatory condition of the lining of the uterus. It is commonly caused by an infection such as tuberculosis or a sexually transmitted disease, however, dietary factors may impact inflammation too.

### Autoimmune conditions

Autoimmune conditions such as Coeliac Disease, Lupus, Type 1 Diabetes, Ankylosing Spondylitis and Multiple Sclerosis are associated with chronic inflammation.<sup>19</sup> Autoimmune markers are common in women with recurrent implantation failure.<sup>20</sup>

### Obesity

In obesity, over-nutrition leads to the accumulation of fat within adipocytes. The increase in adipocyte fat as well as byproducts of triglycerides such as glycerol and free fatty acids results in lipotoxicity and increased rates of adipocyte death. These processes trigger an inflammatory cascade defined by the infiltration of peripheral immune cells into adipose tissue and chronic production of pro-inflammatory cytokines. Consequently, obesity has been linked to chronic low-grade inflammation and increased rates of implantation failure.<sup>21</sup>

## Key nutrients for increasing implantation rates

### Omega 3

A recent study of one hundred women undergoing Assisted Reproductive Therapy found that women who had a higher intake of omega 3 in their diet, had higher rates of implantation than those who consumed less omega 3.<sup>22</sup> Although, research seems to suggest that it's not just omega 3 that's helpful... replacing saturated fats with unsaturated fats seems to be beneficial for implantation in general.<sup>23</sup>

### Zinc

Emerging research suggests that zinc may be particularly important for implantation.<sup>24</sup> Furthermore, high blood copper levels have been shown to be problematic when it comes to implantation and increasing the zinc to copper ratio has been shown to be a good way to improve this.<sup>25</sup> Foods with a good zinc to copper ratio include Brazil nuts, eggs, wheatgerm and oysters.

### Melatonin

The emerging evidence has found that circadian rhythm deregulation followed by low circulating melatonin is associated with low implantation rates and difficulties to maintain pregnancy.<sup>26</sup> Based on the fact that irregular production of maternal and placental melatonin is related to recurrent spontaneous abortion and maternal/fetal disturbances, melatonin replacement may offer an excellent opportunity to restore normal physiological function of the affected tissues. By alleviating oxidative damage in the placenta, melatonin favors nutrient transfer and improves vascular dynamics at the uterine-placental interface.

## Bromelain

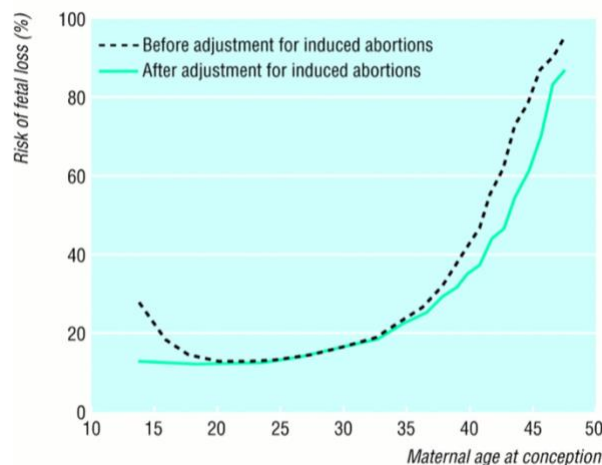
If you delve into any of the popular fertility blogs, talk to other women going through IVF or even do a 'Google' search, you'll come across pineapples being promoted as an A-grade diet pregnancy hack. The advice is framed along these lines: if you eat a whole pineapple, including the core, before and after the day of implantation then the chance of a successful implantation goes up. So, the big, big question is: does it work?! Unfortunately, there is zero scientific evidence to show that pineapples help with embryo implantation during IVF. Like any myth, there is a potential element of truth to it. It is possible, MAYBE, that pineapples could help with embryo implantation. Bromelain is an enzyme found naturally in pineapples, and the most concentrated source of bromelain is found in the core, which is why advice is to be eating the core, rather than just drinking the juice or eating the fleshy outer fruit. The interest in bromelain comes from its potential to reduce inflammation in the body, including in the uterus. It is also a mild blood thinner which some believe can aid in implantation. Interestingly, many doctors prescribe aspirin to women to help with implantation because it is also a blood thinner. But from that connection, you can see why pineapples have attracted interest.

## Trying again post miscarriage

Miscarriage is a common complication early in pregnancy affecting 15 – 20% of all women and couples who successfully conceive.<sup>27</sup> The risk of miscarriage increases with age rising from approximately 10% in women aged 20 – 24 years to over 70% in women 45 years and older.<sup>28</sup> The steepest increase occurs in women from 35 years of age (Figure 1). Miscarriage can be classified into three sub-types based on when the loss occurs:

- 'Biochemical loss' or 'chemical loss' - Loss before 6 weeks gestation
- 'Early pregnancy loss miscarriage' - < 12 weeks gestation
- 'Late pregnancy loss miscarriage' - > 12 weeks and < 21 weeks.<sup>29</sup>

Regardless of the timing, miscarriage can be a cause of significant distress for couples with empathy, support and reassurance an important component of clinical management.



**Figure 1:** Risk of fetal loss from spontaneous abortion, ectopic pregnancy, and stillbirth according to maternal age at conception. <sup>28</sup>

### Recurrent miscarriage

Recurrent miscarriage, affects approximately 2 – 3% of all women and couples who experience pregnancy loss and is defined as the loss of three or more pregnancies before 20 weeks gestation.<sup>27</sup> It can affect women with and without a history of successful pregnancy and occurs more frequently in women of advancing maternal age.<sup>30</sup> Although miscarriage risk has been shown to increase with successive pregnancy losses, for couples who experience recurrent miscarriage without a diagnosed cause (approximately 50% of all cases) 77% will have a successful pregnancy in the future.<sup>27</sup> This highlights the importance of reassurance in the care of couples who experience miscarriage.

There are many established causes of miscarriage including genetic abnormalities, endocrine and immunological disorders, anatomical factors, implantation deficiencies, male factors, infection, and lifestyle.<sup>27 29 30</sup> In terms of lifestyle factors, smoking, alcohol, illicit drug use and obesity have all been shown to increase the risk of miscarriage in women.<sup>29</sup> Importantly, paternal lifestyle factors have also been shown to increase miscarriage risk.

### Weight

A meta-analysis conducted in 2008 found that women with a BMI  $\geq 25$  kg/m<sup>2</sup> were more likely to experience miscarriage, regardless of whether conception occurred naturally or via ART (odds ratio, 1.67; 95% confidence interval, 1.25–2.25).<sup>31</sup> However, when the method of ART was stratified further, the likelihood of miscarriage in women with a BMI  $\geq 25$  kg/m<sup>2</sup> was increased after both oocyte donation and ovulation induction but not IVF-ICSI. In the case of ovulation induction, the odds of miscarriage were 5 times higher in women with a high BMI, relative to women with a normal BMI.

Excess weight has also been shown to increase the likelihood of recurrent miscarriage with the odds 1.75 times higher in women with a BMI  $\geq 30$  kg/m<sup>2</sup> relative to women with a normal BMI.<sup>32</sup>

The mechanisms underlying the association between obesity and miscarriage risk are not well understood. In obese men, increased levels of sperm DNA fragmentation and oxidative stress in semen are associated with higher rates of recurrent miscarriage.<sup>33</sup> In women, abnormalities in reproductive hormone profiles, poor oocyte quality and reduced receptivity of the endometrium for fertilisation have all been hypothesized to increase the rate of miscarriage in women.<sup>32</sup>

Lifestyle interventions such as weight loss and their impact on miscarriage risk have yielded inconsistent findings. A recent systematic review and meta-analysis found that lifestyle interventions (VLED, diet and exercise, exercise and counselling) were associated with a small but significant increase in the risk of miscarriage (RR: 1.50, CI: 95% 1.04 to 2.16; I<sup>2</sup>=0; 6RCTs; N=543).<sup>34</sup> However, these authors rated the quality of studies included as low to moderate. In subsequent analyses, removal of one study that was considered low quality and contributed considerable heterogeneity to the meta-analysis found no association between lifestyle interventions and miscarriage risk.

### Suboptimal folate intake

Low folate status in women has been shown to be a risk factor for miscarriage.<sup>35</sup> Epidemiological studies have demonstrated that increasing BMI is associated with low folate intake and reduced serum folate levels.<sup>36</sup> Folate deficiency is also more likely in individuals with gastrointestinal pathologies such as Crohn's disease, coeliac disease and bariatric surgery.<sup>37</sup> Current guidelines

recommend that women who are planning to conceive should take a folic acid supplement of at least 0.4mg daily in the month prior to conception and for the first three months of pregnancy.<sup>38</sup> Where there is an increased risk of adverse outcomes such as neural tube defects, the dose should be increased to 5mg per day. Indications for requiring higher doses of folic acid include certain medications, diabetes, history of neural tube defects and BMI > 35. Individuals with malabsorption issues should also increase their intake to 5mg per day.

### Suboptimal niacin intake

A landmark study undertaken in Australia shows that niacin (vitamin B3) may significantly reduce miscarriage risk.<sup>39</sup> The researchers analysed the DNA of four families where the mothers had suffered multiple miscarriages or their babies were born with multiple birth defects, such as heart, kidney, vertebrae and cleft palate problems. They found mutations in two genes that caused the child to be deficient in a vital molecule known as Nicotinamide adenine dinucleotide (NAD), which allows cells to generate energy and organs to develop normally.

The researchers then replicated these mutations in mice and found they could be corrected if the pregnant mother took niacin supplements. This is particularly important for women who follow a vegan diet, have gastrointestinal conditions or who have severe morning sickness.

### Dietary associations

Italian researchers undertook a case control study for 912 women who were admitted to an obstetric hospital for spontaneous abortion (prior to 12 weeks gestation).<sup>40</sup> The controls were women who gave birth to term infants at the same hospital. The risk of spontaneous abortion was inversely and significantly related to green vegetables, fruit, milk, cheese, eggs and fish consumption. The multivariate odds ratios, for highest versus lowest levels of intake, were 0.3 for fruit, 0.5 for cheese, 0.6 for green vegetables and milk and 0.7 for fish and eggs. Furthermore, a high intake of fat showed a direct correlation with risk of miscarriage.

Similarly, a population-based case-control study from the United Kingdom showed that lower intakes of fresh fruit and vegetables, dairy, and chocolate were associated with increased odds of a spontaneous abortion.<sup>41</sup> However, a prospective cohort study found no correlation between either a 'Fertility Diet', 'Healthy Eating Diet' or 'Mediterranean Diet' and miscarriage risk.<sup>42</sup>

\*Key article to read and discuss: [https://www.ajog.org/article/S0002-9378\(19\)30345-X/fulltext](https://www.ajog.org/article/S0002-9378(19)30345-X/fulltext) and <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286554/>

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