Chapter 1

Introduction

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Most of our focus in producing success using in vitro fertilization technology has been on stimulation regimens and laboratory procedures to maximize outcomes. As these steps have been optimized, we have started to look in other areas for improvement. One of these points of focus is the environment for conception. It has to be recognized that the early embryo is vulnerable at the time of implantation and early fetal development, and this time period needs to be optimal to grow into as healthy a human being as possible. There are genetic effects which we can now sometimes screen for and eliminate, but there are also many environmental effects on gametes and the developing embryo that can affect the successful outcome of, or even the establishment of, a pregnancy. We have now come to understand some of the environmental factors under which the gametes grow and the embryo develops, and which have long-term implications for human development and may also be the basis of disease.

This hypothesis is not new and was first proposed in 1990 by the British epidemiologist David Barker with respect to intrauterine growth retardation, low birth weight, premature birth and their potential relationship to the origins of several diseases in middle age of adult life. Those included are non-insulin-dependent diabetes, hypertension and coronary heart disease. The developmental origins of health and disease hypothesis derived from a study that showed significant association between the occurrence of hypertension and coronary heart disease in middle age with patients who were born with low birth weight. This was presented in Barker's book, *Fetal and Infant Origins of Adult Disease*, in 1992.

We now recognize that parenting begins before conception. Environmental toxins or endogenous metabolic disease, such as nicotine or obesity, can compromise the egg or sperm from either parent and deleteriously effect development even if the intrauterine environment is optimal. Many factors are known to adversely affect gametes, including obesity, poor nutrition, cigarette smoking and some environmental pollutants. Not only should we be concerned about potential toxicants, but also about the deficiency of various nutrients which can be aetiological determinants of obstetrical complications, and paediatric chronic diseases.

There have been attempts at establishing preconception planning either through clinical activities, the print and electronic media or through government action. Some hospitals have established preconception clinics where couples can receive counselling and checking of immunity, immunization, advice on weight reduction and substance withdrawal. Several societies and organizations have proffered guidelines and action plans.

Some proponents of preconception care [1] go as far as suggesting that "With the totality of available scientific evidence that now exists on the potential to modify disease-causing

gestational determinants, failure to take necessary precautionary action may render members of the medical community collectively and individually culpable for preventable illness in children."

Apart from any possible medico-legal issues, we believe that those of us working in assisted reproductive technology, where pregnancies are planned and there is a significant effort and cost in achieving them, should take every effort to ensure every child is born in the very best condition, and has as healthy a life as possible.

It is with this in mind that this volume, *How to Improve Preconception Health to Maximize IVF Success*, is the first in a series of four books on how to improve the outcome of ART.

References

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Chapter 2

The Effects of Nutrition and Micronutrients on Reproductive Success

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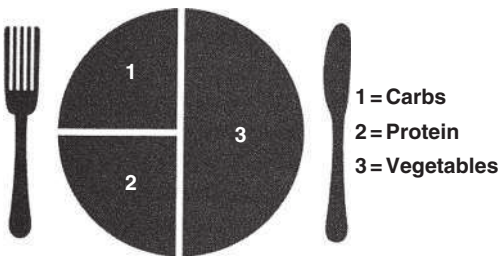
Introduction

Nutrition and lifestyle choices hold implications for general health, as well as real and potential effects on fertility and reproductive health. While the effects of diet on health and risk of chronic disease have been well described, there is relatively little research on fertility *per se*. It is likely that the majority of men and women with subfertility, regardless of weight, have a form of intrinsic insulin resistance that underlies the downstream effects on oocyte and sperm quality [1]. Insulin resistance results in compensatory hyperinsulinemia, which plays an important role in all the manifestations of subfertility, including androgen excess, inflammation, and anovulation in women with polycystic ovarian syndrome (PCOS). Insulin resistance is also associated with markedly increased risk of chronic disease in both men and women. The prevalence of type 2 diabetes, for example, is up to ten times higher among young women with PCOS as among normal women. Maximizing insulin sensitivity through diet and other lifestyle interventions (such as weight loss, increasing physical activity and muscle mass, improving sleep quality and stopping smoking) should be a major target in optimizing outcomes in men and women with subfertility.

Macronutrients – Does Diet Composition Matter?

The benefits of weight reduction in subfertile couples are well documented [2], although the optimal diet composition or macronutrient ratio – proportions of fat, protein, and carbohydrates – may also affect outcomes [3]. High-fat diets are associated with insulin resistance in animal studies, but the evidence is mixed in human studies. Randomized controlled feeding trials show that the most consistent improvements in glucose–insulin homeostasis are seen with diets high in unsaturated fat, rather than saturated fat, monounsaturated fat or carbohydrate [4]. The quality rather than quantity of fat (saturated vs. unsaturated) is therefore a more important consideration. Dietary guidance for infertile couples should emphasize *moderate* intake of fat (30–35 percent energy), *not* low fat intake, and encourage monounsaturated and polyunsaturated sources of fats and oils, including nuts, olive oil, rice bran and canola oil, fatty fish (e.g., salmon) and avocados.

The amount and quality of carbohydrate may be particularly important in the context of fertility because both factors directly affect postprandial glycemia and insulinemia. Higher intake of fiber from grains and cereals improves insulin sensitivity within



On the plate

1. Carbohydrate-rich foods should make up about a quarter of the plate. Include breads and cereals (choose the **low GI** varieties), and other starchy foods such as potatoes, sweet potatoes, legumes, sweet corn, pasta, noodles and rice.
2. Protein-rich foods should take up another quarter of the plate. Include lean red meat, chicken and poultry, any type of fish, eggs, tofu, legumes.
3. Vegetables should take up half the plate (or more if you are hungry). Use as many colours as possible – green leafy and salad vegetables, carrots, green beans, peas, broccoli and cauliflower, zucchini, baby squash, onions, leeks, fennel and asparagus.

   They provide not only micronutrients, but also anti-oxidants that reduce inflammatory responses.

On top of the plate

Sprinkle black and white chia seeds to increase your fibre intake
Top with small amounts of feta, parmesan and other cheeses that add flavour

Outside the plate

Think fruit (whole is better than juice)
Milk and milk products such as yogurt

Figure 2.1 The plate model of a balanced, healthy meal
Reproduced with permission from The Low GI Diet Diabetes Handbook, Hachette Australia 2012

72 hours. Acutely, meals with a lower glycemic load have been shown to reduce postprandial glycemia and insulinemia by virtue of having less carbohydrate (but more protein and/or fat) and/or carbohydrates sources with a low glycemic index (GI). In meta-analyses of randomized controlled trials, diets with a lower glycemic load were found to reduce fasting insulin (a measure of insulin resistance) and C-reactive protein (CRP), a measure of chronic low-grade inflammation [5]. Lower glycemic load diets may improve oocyte and sperm quality.

While there is now strong evidence that both high carbohydrate and low carbohydrate diets are effective for weight loss and weight maintenance, the degree of carbohydrate restriction for long-term optimal health is still contentious. In observational studies, *very low* carbohydrate (25 percent energy), high protein diets are associated with higher mortality and higher risk of type 2 diabetes and cancer [6], suggesting caution. Instead, a small degree of carbohydrate restriction (~45 percent energy) and modestly increased protein (~25 percent energy) and fat (~35 percent energy) will facilitate weight reduction and weight maintenance as well as long-term health. Figure 2.1 shows a plate model of how the quantity and quality of carbohydrates, fats and proteins can be visualized.

Low GI Diets

The glycemic index (GI) is a metric used to categorize carbohydrate foods according to their effects on postprandial blood glucose levels on gram-for-gram carbohydrate basis. Food with a low GI includes nearly all kinds of beans and legumes, pasta, dairy products, and fruit. Only some brands of breads, breakfast cereals, and rice have a low GI, as shown in Table 2.1.

The capacity of dietary carbohydrates to increase postprandial glycemia is particularly relevant to optimizing metabolic and clinical outcomes in PCOS and other subfertile women. We showed that independently of the degree of weight loss, an *ad libitum* low GI diet had benefits over and above those of a conventional healthy diet matched for macronutrient and fiber content [8]. With only modest weight loss (~5 percent of body weight), the low GI diet provided a three-fold greater improvement in whole-body insulin sensitivity as calculated from responses to a 75 g oral glucose challenge, and greater improvement in hemostasis as judged by changes in serum fibrinogen. Clinically, a larger proportion of subjects on the low GI diet reported improved menstrual regularity (95 percent vs 63 percent) and better "emotion" scores on a questionnaire designed to detect changes in quality of life. By contrast, both the low GI and the conventional healthy diet led to similar improvements in blood lipids, androgenic hormones, markers of inflammation, and other measures of quality of life.

Prescribing a low GI diet for subfertile couples can have other advantages. Currently, a large proportion of pregnant women do not meet recommended intakes of folate, iron, riboflavin, iodine, calcium, magnesium, potassium, and fiber. The large majority also exceed the recommended intake of saturated fat. In our own studies, we found that women who consumed a diet with a lower GI were more likely to have a higher quality diet, with higher intakes of fiber, dietary folate, potassium, and calcium [9]. Surprisingly, those who consumed more grains and cereal products had poorer diets, with lower intakes of riboflavin, potassium, and dietary folate. Similar observations relating lower GI food patterns to higher diet quality have been made in various population groups.

At no other time in life is the rate of growth as fast as it is in pregnancy. Increased tissue deposition and cellular metabolism correspond to increased demand for nutrients. But the solution is not as simple as eating more of the same diet because the proportional increase in demand for micronutrients is much greater than the need for additional calories. Indeed, a recent meta-analysis suggests that modern women do not eat significantly more energy (calories) in late versus early pregnancy [10]. Instead, they appear to reduce physical activity energy expenditure to compensate for the extra energy demands of pregnancy.

The Case for Micronutrient Supplements

Compared to the past, modern sedentary lifestyles require little in the way of energy expenditure. Maintaining an ideal weight therefore means that energy intake from food must be kept relatively low, increasing the risk that even a conventional healthy diet is not adequate for successful pregnancy outcomes. This imposes the need for micronutrient supplements before and during pregnancy. However, the composition of vitamin and mineral supplements varies markedly and very few have scientific evidence for improving fertility rate *per se*. In one instance, a supplement was found to improve pregnancy rates in infertile women in a randomized controlled trial: 14 of the 53 women in the supplement

Table 2.1 Glycemic index (GI) values of common carbohydrate foods. Data are average results from available values listed in the International Tables of GI and GL adapted from international tables of GI and GL [7].

High carbohydrate foods		**Breakfast cereals**		**Fruit & fruit products**	
White wheat bread	75	Cornflakes	81	Apple	36
Wholemeal bread	74	Wheat flake biscuits	69	Orange	43
Specialty grain bread	53	Porridge, rolled oats	55	Banana	51
Unleavened wheat bread	70	Instant oat porridge	79	Pineapple	59
Wheat roti	62	Rice porridge	78	Watermelon	76
Chapatti	52	Muesli	57	Dates	42
Corn tortilla	46			Peaches, canned	43
White rice, boiled	73	**Vegetables**		Strawberry jam/jelly	49
Brown rice, boiled	68	Potato, boiled	78	Apple juice	41
Barley	28	Potato, instant mash	87	Orange juice	50
Sweet corn	52	Potato, French fries	63		
Spaghetti, white	49	Carrots, boiled	39	**Sugars**	
Spaghetti, wholemeal	48	Sweet potato, boiled	63	Fructose	15
Rice noodles	53	Pumpkin, boiled	64	Sucrose	65
Couscous	65			Glucose	103
		Legumes		Honey	61
Dairy products & alternatives		Chickpeas	28		
Milk, full fat	39	Kidney beans	24	**Snack products**	
Ice cream	51	Lentils	32	Chocolate	40
Yoghurt, fruit	41	Soya beans	16	Potato crisps	56
Soy milk	34			Soft drink/ soda	59
Rice milk	86			Rice crackers/ crisps	87

group became pregnant (26 percent) compared to four of the 40 women in the placebo group (10 percent) [11]. Some micronutrients are more important that others, not only because they are critical for optimum fetal growth, but because modern diets are nearly always deficient. There is now a large body of evidence for supplements containing specific amounts of iodine, folate and iron.

The Case for Iodine

Iodine is a chemical element that widely exists in the natural environment and is an important nutrient for humans. Like other micronutrients, it is needed only in small amounts for human health. The only known physiological function of iodine is that it is an integral component of the thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4). The absorbed dietary iodine (as inorganic iodide) is predominantly taken up by the thyroid gland for thyroid hormone synthesis and stored in the thyroid gland in a form of protein-bound iodine and in extra-thyroidal tissues, such as the mammary gland. Thyroid hormones regulate growth and metabolic rate in humans and are essential for optimal brain and physical development of the fetus and infant. The fetus is totally dependent on maternal T4 until late in gestation when the developing fetal thyroid gland becomes functional before birth. Similarly, the breastfed infant is entirely dependent on iodine in the mother's milk to ensure adequate iodine supply, hence normal thyroid function. It is critically important that the mother has sufficient total body iodine store before conception, during pregnancy and when breastfeeding for growth and development of her fetus and young child.

Iodine Requirements

Iodine requirements increase dramatically during pregnancy, in order to: 1) meet the ~50 percent increase in demand of the mother's thyroid hormone production early in gestation; 2) ensure trans-placental transfer of T4 and iodine to the fetus, since the early part of fetal development is totally dependent on the maternal T4 transfer and iodine needs to be transferred to the fetus for fetal thyroid hormone production in later gestation; and 3) compensate for increased clearance of iodine by the kidney during pregnancy. Reaching and maintaining sufficient maternal thyroid iodine stores before pregnancy will protect the fetus. If the mother's preconception iodine nutrition is adequate, her iodine stores will be sufficient to support the increased demand for thyroid hormone production and the trans-placental transfer to her fetus. If the maternal thyroid gland cannot meet the demands of pregnancy on thyroid hormone production due to insufficient dietary iodine intake, there are likely to be adverse obstetric and fetal consequences.

Sources of Iodine

The main dietary sources of iodine are milk and dairy products, seafood, iodized salt, and processed foods with added iodized salt, such as bread. Cereals, fruits, and vegetables are generally poor sources of iodine. Iodine also presents in some medications (such as amiodarone), medical imaging contrast agents, and topical sanitizing productions (such as povidone). Recommended daily intakes of iodine for women >18 years vary from as low as 100 μg/day to 150 μg/day as recommended by WHO, UNICEF, and International Council for the Control of Iodine Deficiency Disorders (ICCIDD). As iodine requirements increase

dramatically during pregnancy, the estimated average requirement for pregnant women is increased to 160 μg, and the RDA to 220 μg per day. However, WHO, UNICEF, and ICCIDD recommend 250 μg daily for pregnant women [12].

Dietary iodine is readily absorbed from the gastrointestinal tract and enters the circulation in the form of iodide. Iodide is mostly cleared from the circulation by the thyroid gland and kidney. Iodine nutrition status in a population, therefore, is assessed by a proxy indicator, the median urinary iodine concentration (UIC). For non-pregnant and non-lactating women the median UIC <100 μg/L indicates insufficient iodine intake. For pregnant women the median UIC <150 μg/L is defined as insufficient intake; UIC of 150 μg/L corresponds to a daily iodine intake of ~250 μg, the recommended daily intake for this population group [12]. Estimation of iodine intake from UIC is based on assumptions that the urine output is consistent and the bioavailability of iodine is about 90 percent. Urinary iodine concentration is less precise for assessing iodine nutrition in an individual as it only reflects iodine intake in recent days. Individual urine results must be interpreted in the context of the dietary history. Excretion of iodine in the urine is subject to influences of many factors, such as variation in dietary intake, body weight, seasonality, hydration level and urine output. Estimation of iodine intake by documentation of food composition assessment is frequently confounded by variations in food iodine content and lack of information in country-specific food composition tables. Nonetheless it is used as an alternative to calculations based on UIC to provide an assessment of dietary iodine intake.

Iodine Deficiency Disorders

The term *Iodine Deficiency Disorders* (IDD) was first introduced in 1983 to emphasize that iodine deficiency can affect human beings at all stages of the life cycle and has a broad spectrum of adverse effects. These include mental and physical impairment, disturbed thyroid function and goiter [12]. Iodine deficiency is not confined to developing countries; increasingly evidence shows it has re-emerged in developed countries. For over four decades, milk contaminated with trace amounts of iodine residues from iodophors, iodine containing sanitizing agents, used in the dairy industry was the main source of iodine in many developed countries, contributing at least 50 percent of the daily intake. As a consequence of the replacement of iodophors by other agents in the dairy industry in the 1990s, the iodine content in milk has been drastically reduced and iodine deficiency has re-emerged in countries such as Australia and New Zealand [13]. Milk was once the source of adequate iodine nutrition in the United Kingdom from iodine added to cattle feed to improve cow's milk production. Due to a reduction in milk consumption, iodine deficiency has been reported, particularly in adolescent girls and women of reproductive age in the UK. The general population in the USA and Canada are iodine sufficient; however, the more recent National Health and Nutrition Examination Surveys data suggest pregnant women in the USA are also mildly iodine deficient [13].

Severe maternal iodine deficiency and hypothyroidism have been associated with impaired neurological development in the offspring but the effect of mild-moderate maternal iodine deficiency on the offspring is difficult to quantify [14]. Recent observational studies suggest significant decreases in IQ and school performance in spelling, grammar, and overall literacy of children (8 to 10 years) born to mothers whose urinary iodine concentration was less than 150 μg/L during pregnancy [15]. These studies support the

argument that even mild maternal iodine deficiency can result in neurocognitive impairment in the offspring of those mothers.

Like iodine deficiency, excessive iodine intake can also cause changes in thyroid function. Most individuals can tolerate high level of dietary iodine intakes relative to the recommended amounts. For example, in healthy non-pregnant and pregnant women the upper limit of nutrient for iodine is 1,100 µg/day, i.e., iodine intakes up to 1,100 µg/day are considered to be safe. For individuals who have underlying defects in thyroid hormone synthesis, such as those with Hashimoto's thyroiditis, excessive iodine intake can have adverse effects.

Increasing Iodine Intake

The primary strategy recommended by the WHO for the prevention and control of iodine deficiency is universal salt iodization. Globally, about 70 percent of all households currently have access to adequately iodized salt. In 2009, Australia and New Zealand implemented the mandatory iodine fortification of bread in commercial bakeries because only a small proportion of people purchase iodized salt and the food industry, as a whole, does not use iodized salt in food production and preparation. Denmark and Belgium also control iodine deficiency in their populations using iodized salt in bread making. In one serving of bread (two slices of non-organic bread, approximately 60 grams) the estimated iodine content is 28 µg. Despite the reduction of iodine content in cow's milk, one serving of milk (250 mL) still contains approximately 57 µg iodine and is a good source of dietary iodine.

There is no doubt that adequate iodine intake before and during pregnancy achieved by a diverse healthy diet is the desired option. In countries where iodine deficiency is prevalent but universal salt iodization has not been implemented, iodine supplementation is the recommended solution for women planning on pregnancy and pregnant women. Concerned by the possibility of inadequate iodine intake among pregnant women, the American Thyroid Association recommended iodine supplementation during pregnancy and lactation in the USA and Canada in 2006. Informed by the fact that mandatory iodine fortification of bread is not likely to provide adequate dietary iodine to this special subgroup of the population, countries where iodine deficiency is re-emerging, such as Australia and New Zealand, recommend that all women who are considering pregnancy, during pregnancy and lactation, should take a 150 µg/day iodine supplement, with the caveat that women with preexisting thyroid disorders should seek advice from their medical practitioners before taking a supplement. Ideally, iodine supplementation should commence three to six months before conception and continue until the infant is weaned to establish an appropriate iodine supply for pregnant and breastfeeding mothers.

The Case for Iron

Iron is a mineral that is present in many foods and is an essential bio-element for most forms of life, from bacteria to mammals. Its importance lies in its ability to mediate electron transfer and it plays a vital role in the catalysis of enzymatic reactions that involve electron transfer (reduction and oxidation or "redox" reactions). This controls the release of energy from cells. It is an essential component of a number of proteins including hemoglobin and myoglobin, required for red blood cell production and transportation of oxygen throughout

the body. Oxygen is transported from the lungs to the rest of the body bound to the heme group of hemoglobin in erythrocytes. In muscle cells, iron binds myoglobin, which regulates its release. It is also important for normal growth, neurodevelopment, and immune function.

Dietary iron is found in two main forms: heme and non-heme. In animal foods, iron is often attached to proteins called heme proteins, and referred to as heme iron. In plant foods, iron is not attached to heme proteins and is classified as non-heme iron. Heme iron contributes to approximately 10–15 percent of total iron intakes in Western populations and is better absorbed than non-heme iron. The amount of iron available directly relates to how much is stored in the body. Almost two-thirds of the body's iron is found in hemoglobin in circulating red blood cells. About a quarter of the body's iron is found in the liver and reticulo-endothelial system in ferritin or hemosiderin which are readily metabolized. The remaining iron is in the myoglobin of muscle tissue and several enzymes that are necessary for oxidative metabolism and other cell functions.

What Happens When Iron is Deficient?

Inadequate iron in the body can impair aerobic metabolism by decreasing the delivery of oxygen to tissues and reducing the capacity of muscles to use oxygen for the oxidative production of energy. Iron deficiency is the most common deficiency state in the world, affecting more than two billion people globally. Although it is particularly prevalent in less-developed countries, it remains a significant problem in the developed world, even where other forms of malnutrition have almost disappeared. Iron deficiency is defined as a condition in which there are no mobilizable iron stores and in which signs of a compromised supply of iron to tissues are noted. The more severe stages of iron deficiency are associated with anemia.

Anemia is defined as an Hb concentration below the reference range (specific for age, sex, and gestation) for the laboratory performing the test. The WHO defines anemia as an Hb level below 130 g/L in men, 120 g/L in women, and 110 g/L in pregnant women and preschool children. Iron deficiency is the most common cause of anemia in pregnancy [16]. It occurs in approximately 56 percent of pregnancies in developing countries and 12 percent in developed countries like Australia; however, particular ethnic groups have increased prevalence: it ranges between 25–40 percent in Australian Aboriginal women and children [16]. This increase in the prevalence of iron deficiency in more disadvantaged populations is consistent with data from the National Health and Nutrition Examination Survey 1999–2000 in the US where the prevalence of iron deficiency among women aged 12–49 years was 9–16 percent overall but three times higher among minority females in the same age group.

Research suggests that iron stores at the time of conception are a strong indicator of a woman's risk for iron-deficiency anemia later in pregnancy. Currently 15 percent of non-pregnant women of reproductive age in developed countries have anemia, with iron deficiency anemia the major cause. Low preconception hemoglobin and ferritin levels increase the risk of poor fetal growth and low birth weight. A longitudinal cohort study demonstrated lower risk of ovulatory infertility in women who consumed iron supplements and higher levels of non-heme iron [17]. Iron appears to also be important for male fertility, with a recent small study demonstrating significant improvement in