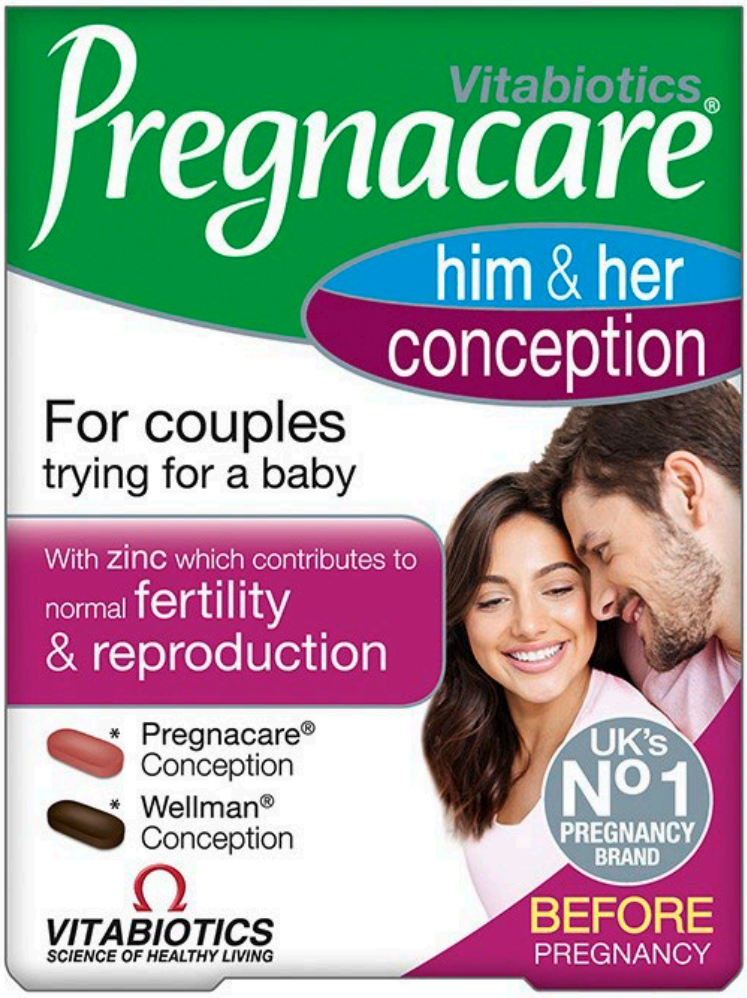
VITABIOTICS
SCIENCE OF HEALTHY LIVING

Introduction to
Pregnacare Him & Her Conception



Professional Information
Not for Public Distribution

Updated February 2022

Contents

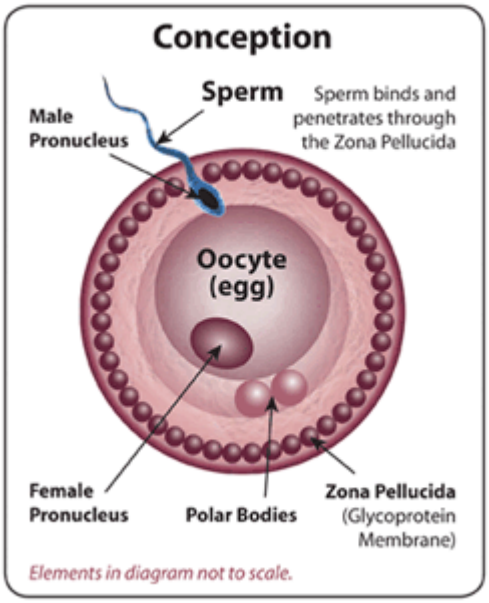
This document is for internal use only to provide an introduction to the product, its formulation and supporting scientific evidence. Please note the content in this product dossier is not EFSA compliant and is not intended for use in any commercial context in the EU.

Introduction

The makers of Pregnacare®, the UK's leading pregnancy supplement, have developed Pregnacare Him & Her Conception to provide advanced nutritional support when trying for a baby. Pregnacare Him & Her Conception nutritional tablets are specifically designed to support the nutritional requirements of men and women who are trying to conceive.

Pregnacare Conception also includes vitamin B12 and folic acid at 400µg, the exact recommended level to help safeguard the early stages of foetal development, plus zinc which is scientifically proven to support fertility and reproduction.

Fertility problems are much more common than generally recognised with a third of couples struggling to conceive naturally. It has also been estimated that at some time in their reproductive lives at least a quarter of couples experience a period of infertility (inability to conceive) lasting over 1 year[1]



It is important for couples to be in the best possible health nutritionally, ideally at least 6 months before a baby is conceived. The sperm and ovum are formed well in advance of fertilization and need to be provided with the best nutrients possible for when they combine. The effect of nutrition on conception rates has been rigorously studied and shows that without adequate nutrients the chances of healthy ovulation, fertilization and embryo implantation are compromised.

More than 2.5 million men in Britain may be suffering from fertility problems, with high rates of smoking, stress and drinking believed to be contributory factors. The quality and number of sperm that men produce has declined in the past 30 years, with male infertility accounting for about a third of couple's problems conceiving.

Summary of Key Ingredients

As part of helping to ensure a healthy conception, couples are now routinely counselled to look at their lifestyle and diet as practical measures which can help to improve their fertility and their chances of success, including nutritional supplementation. It is now widely accepted that nutritional deficiencies can have a direct impact on male as well as female fertility. Furthermore, research in this area indicates that certain specific nutrients e.g. Zinc, Co-Enzyme Q10, vitamin C & E, lycopene and amino acids can all affect fertility in men. Folic acid is also important in men for sperm health.

In women, nutritional deficiencies of folic acid, vitamin B6, vitamin C, vitamin D, vitamin E, iodine, zinc, selenium, iron and inositol have been shown to affect conception rates.[2] For couples who are serious about conception and the very best start for their developing baby, it is recommended that both partners address their diet and nutrition.

There is a clear scientific rationale and growing awareness of the need for preconception care. Pregnacare Him & Her Conception dual pack now provides the opportunity for couples to take a simple, balanced daily formula specifically developed for reproductive health as well as overall wellbeing.

1. Gunnell D.J. and Ewings P. Infertility prevalence, needs, assessment and purchasing. *Journal of Public Health Medicine* 1994; 16: 29-36

2. Kai J. Buhling and Donata Grajecki. The effect of micronutrient supplements on female fertility. *Current Opinion in Obstetrics and Gynecology*

Fertility Facts for Women

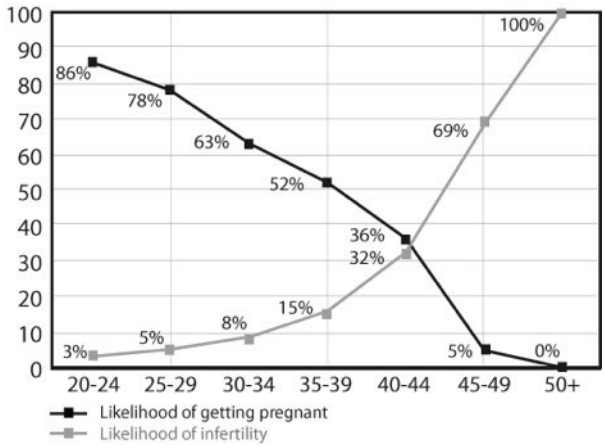
Age and fertility

According to research women are leaving it later to start a family. The Office of National Statistics has reported that since the 1980s the rates for women giving birth at age 30 or over have gone up, while the rates for women giving birth aged under 30 have fallen.

Fertility falls more sharply for women as they age than for men. Women are most fertile between the ages of 20 and 24 years - as women grow older the likelihood of getting pregnant falls while the likelihood of infertility rises sharply. Men can remain fertile for much longer but male fertility still declines with age, although less dramatically.

Chart: Pregnancy rates over the course of one year

Both of the line graphs are for women with normal reproductive function.



Source: **Management of the Infertile Woman** by Helen A. Carcio and **The Fertility Sourcebook** by M. Sara Rosenthal

Fertility factors

As women get older, there are a number of factors that can make it more difficult to conceive.

Fertility factors that change include:

- Ovarian reserve - this is the number of functioning follicles left in the ovaries. As women get older they have fewer viable eggs left; in cases of early menopause, the eggs run out much sooner than usual.
- Menstrual cycle - as women approach the menopause their menstrual cycles can become irregular and shorter.
- Lining of the womb - the endometrium may become thinner and less hospitable to a fertilised egg.
- Mucus secretions - vaginal secretions can become less fluid and more hostile to sperm.
- Diseases affecting the reproductive system - some conditions can damage the reproductive organs as time passes, or worsen if not treated properly, including endometriosis, PCOS, Chlamydia.
- Chronic illnesses - some illnesses can have a negative impact on fertility.

Fertility Facts for Men

When couples decide to try for a family, it is not only women who need to look after their diet and lifestyle in order to maximise their health and support conception. Male nutritional status may also significantly influence healthy strong viable sperm and the likelihood of conception.

Infertility is defined as the failure to become pregnant after one year of unprotected, well-timed sexual intercourse. In men, infertility is usually associated with a decrease in the number, quality, or motility (movement) of sperm.

There are many factors that can decrease or cease sperm production, which can include:

- Illness
- Excessive Caffeine
- Stress
- Excessive alcohol consumption
- Street and certain prescription drugs
- Some over the counter medications
- Injury to the testicles
- Excessive heat to the testicles
- Micronutrient deficiencies

IF PREGNANCY IS NOT ACHIEVED AFTER ONE YEAR OF REGULAR, UNPROTECTED SEX, BOTH SEXUAL PARTNERS SHOULD BE TESTED FOR POSSIBLE INFERTILITY PROBLEMS. LOW SPERM COUNT, DECREASED MOTILITY, OR ABNORMAL SHAPE OF THE SPERM ARE RESPONSIBLE FOR INFERTILITY IN ABOUT 40% OF THESE COUPLES. FEMALE CAUSES ACCOUNT FOR 40% OF INFERTILITY CASES, AND 20% ARE ATTRIBUTED TO A COMBINATION OF BOTH.

At least one in five of all couples are affected by some degree of infertility. A sobering thought but fortunately many of these couples can benefit from help. Statistics vary but it would seem that around **30% of men are sub-fertile** and at least **2% of men are totally infertile**. Furthermore there is a great scientific debate going on just now about evidence suggesting that male fertility is decreasing markedly as a result of modern lifestyles.
(source: http://www.malefertility.co.uk/statistics.html)

Product Information

Pregnacare Him & Her Conception is an extra value dual pack containing Pregnacare Conception and Wellman Conception nutritional tablets specifically designed to support both men and women who are trying for a baby and concerned about their fertility.

Pregnacare Conception tablets for women

A carefully balanced comprehensive formulation of micronutrients for the maintenance of healthy fertility in women including specific fertility supporting nutrients including the following:

Folic Acid
Pregnacare Conception provides 400µg folic acid, the exact level recommended by the UK Department of Health for all women who are trying to conceive. As well as the healthy development of the foetal neural tube, folic acid may also play a role in conception, and is required in the first days and weeks of life, before you are even aware that you are pregnant. Studies show that folic acid supplementation should ideally start before conception.

Inositol
A precursor to Nitric Oxide (NO) may also help aid conception by dilating blood vessels and maintaining follicular blood flow to reproductive organs. This micronutrient may also help induce endometrial secretion, thus creating a healthy uterus lining during implantation time. A study by Morlin and Hammarstrom in 2005 found that women administered with NO had markedly increased cervical secretion compared with the control group who showed no changes.

Co-Enzyme Q10

Produced and used in all cells in the human body. By supplementing Co-Q10 eggs have a better chance of sufficient energy from its mitochondria to propel healthy growth. Antioxidant protects cells' DNA from damages from oxidative stress. Free radicals can cause damage to the egg cell's DNA, which can also lead to egg quality problems.

N-acetyl cysteine (NAC)
This is a precursor to glutathione, which is an important naturally occurring antioxidant, well known as a mucolytic agent to thin mucus secretions. In addition, Inositol levels may be associated with pregnancy outcome, as it has been suggested that women with low levels of this nutrient may have a higher risk of spontaneous abortion. Low inositol levels, may be a cause of some neural tube defects therefore supplementation can help maintain healthy levels.

Vitamin B12
Part of the B complex group of vitamins, it has been found that B12 supplementation can maintain healthy ovarian function and reproductive health.**Vitamin C**

Can help cervical mucus to become more plentiful, which is important to help sperm survive in the body and be transported to the egg for fertilisation.

Antioxidant minerals with natural vitamin E
Important co-factors in antioxidant enzymes, to help protect genetic material from free radical damage.

Vitamin D
Vitamin D deficiency in pregnancy can have devastating health consequences in the newborn and infant including hypocalcaemic seizures, dilated cardiomyopathy, heart failure and death. All health consequences of nutritional rickets and osteomalacia are easily prevented with vitamin D supplementation. Lack of robust supplementation policies and implementation has led to the resurgence of nutritional rickets and a high prevalence of vitamin D deficiency in ethnic risk groups in certain high-income countries. (*British Journal of Midwifery, May 2020*)

Research has shown that Vitamin D plays an important role in regulating the mother's immune system via the placenta in pregnancy. This supports evidence that vitamin D deficiency in pregnancy may affect placental health and increase the risk of other complications.

Wellman Conception Tablets For Men

It is now known that folic acid is not only essential for women who are planning a baby but men as well. As well as folic acid, Wellman® Conception provides a potent blend of antioxidants, vitamins, and minerals which have been specifically chosen for their role in male reproductive function and health. These include the following:

Peruvian MACA Extract
Sourced from the Peruvian herbaceous plant, this organic source Maca contains important nutrients including amino acids and fatty acids, which are essential for male reproductive health.

Co-Enzyme Q10
Acts as an antioxidant and energy-releasing agent and is thought to stabilize the integrity of the sperm flagella.

Folic Acid
Studies suggest that supplementation of folic acid along with zinc supports sperm health.

Lycopene
Highly regarded for its exceptional antioxidant properties, nutritional studies have shown intake of Lycopene linked to prostate health.

Siberian Ginseng Extract
Widely used to help maintain overall male vitality.

Pine Bark Extract

A highly effective antioxidant which may play a role in protecting sperm. Free radicals (responsible for oxidative cell damage) are said to be responsible for 40 percent of sperm damage.

When to use Pregnacare Him & Her Conception
Men and women should use Pregnacare Him & Her Conception as soon as they start trying for a baby. To help build the body's nutritional stores it can even be taken for 3-6 months before you start to try for a baby. Once you have confirmed you are pregnant, women can continue to use up any remaining Pregnacare Conception tablets, before moving on to Pregnacare Original, Plus or Max, which are specially formulated for the remainder of your pregnancy and during breastfeeding. Men can move onto Wellman Original tablets which provide a comprehensive formulation of over 28 essential bio-elements to help maintain general health and vitality in men of all ages.

Pregnacare

Vitabiotics Pregnacare®

UK's No 1 Pregnancy Supplement Brand

An important history of Pregnacare® pioneering the vital use of Folic Acid & Vitamin B12 in pregnancy

1980 Multivitamin supplementation is first shown to reduce the risk of Neural Tube Defects (Spina bifida) in the newborn.[1]
The Lancet, Volume 315, Issue 8164, p339–340, 16 February 1980.

1983 Further evidence published on multivitamins and a significant effect in the prevention of Spina bifida.[2]
The Lancet, Volume 321, Issue 8332, p1027-1031, 7 May 1983.

1988 **Pregnacare® tablets is launched**; the first comprehensive multivitamin formula for pregnancy with 400mcg folic acid and 6mcg vitamin B12.

1991 **Folic acid is specifically identified** to protect against Spina bifida, but **on its own has only a 72% protective effect.**[3]
The Lancet, Volume 338, Issue 8760, p131–137, 20 July 1991.

1993 **Vitamin B12 is also identified as an "independent risk factor"** in the prevention of Spina bifida.[4]
Q J Med, Volume 86, Issue 11, p703-708, 1 November 1993.

1995 **UK Department of Health** & Health Education Authority launch the **first national folic acid awareness campaign.**

2012 **The Prof. Scott report** recommends taking vitamin B12 with folic acid as **more effective in NTD† prevention than folic acid alone.**[5]
Professor J.M. Scott report, Biomedical Sciences Institute, Trinity College, Dublin, Ireland.

2012 Supported by **Pregnacare®**, the UK's leading association for Spina bifida **launches the first official recommendation for vitamin B12.**
"Shine calls on all women who may become pregnant to take a daily supplement containing 400mcg of folic acid and at least 2.5mcg of B12."

The **ONLY** vitamin company to receive **The Queen's Award For Innovation**

www.pregnacare.com

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Pregnacare

Vitabiotics Pregnacare®

UK's No 1 PREGNANCY SUPPLEMENT BRAND

1. Possible Prevention of Neural Tube Defects by Periconceptional Vitamin Supplementation

R.W. Smithells, S. Sheppard, C.J. Schorah, M.J. Seller, N.C. Nevin, R. Harris, A.P. Read, D.W. Fielding

The Lancet, Volume 315, Issue 8164, p339–340, 16 February 1980.

Of a sample of mothers who had previously given birth to one or more infants with a NTD, 5% of infants/foetuses from mothers that were not given periconceptional multivitamin supplementation developed a NTD. Only 0.6% of infants/foetuses of fully supplemented mothers had NTDs.

2. Further Experience of Vitamin Supplementation for Prevention of Neural Tube Defect Recurrences

R.W. Smithells, N.C. Nevin, M.J. Seller, S. Sheppard, R. Harris, A.P. Read, D.W. Fielding, S. Walker, C.J. Schorah, J. Wild

The Lancet, Volume 321, Issue 8332, p1027-1031, 7 May 1983.

Of a sample of mothers with a history of NTDs, significantly fewer foetuses had NTD recurrences when supplemented with a multivitamin. After one previous NTD, recurrence rates were 0.5% for fully supplemented (FS) mothers and 4.2% for unsupplemented (US) mothers: after two or more previous NTDs, 2·3% for FS and 9·6% for US.

3. Prevention of Neural Tube Defects: Results of the Medical Research Council Vitamin Study

N. Wald, J. Sneddon

The Lancet, Volume 338, Issue 8760, p131–137, 20 July 1991.

This ground-breaking trial proved that if taken around the time of conception, supplementation with folic acid can help to prevent NTDs. The trial group that took supplementation with folic acid had a 72% protective effect from NTDs. Recommendations following this study:

• Folic acid supplementation starting before pregnancy for all women who have had an affected pregnancy.

• Public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

4. Maternal Plasma Folate and Vitamin B12 are Independent Risk Factors for Neural Tube Defects

P.N. Kirke, A.M. Molloy, L.E. Daly, H. Burke, D.G. Weir, J.M. Scott

Q J Med, Volume 86, Issue 11, p703-708, 1 November 1993.

Blood was taken at the first antenatal clinic from **56,049 pregnant women**. Plasma folate and plasma B12 were independent risk factors for NTDs. Recommendations following this study:

• Consideration should be given to including vitamin B12 as well as folic acid in any programme of supplementation or food fortification to prevent NTDs.

5. Addition of Vitamin B12 to Folic Acid Supplements to Optimise the Prevention of Spina Bifida and Other Neural Tube Defects.

J.M. Scott Biomedical Sciences Institute, Trinity College, Dublin, Ireland.

Report for Shine.

A new report by Professor J.M Scott, a world authority on vitamin B12, calls for all women who may become pregnant to follow updated pre-conceptual supplement recommendations, which could further reduce the number of pregnancies affected by NTDs. "Taking vitamin B12 alongside folic acid may be more effective in NTD prevention than taking folic acid alone."

Supplemental folic acid intake increases maternal folate status. Low maternal folate status is a risk factor in the development of neural tube defects in the developing foetus.**

* Nielsen GB ScanTrack Total Coverage Value Sales 52 w/e 25 April 2015.

** The beneficial effect is obtained with a supplemental folic acid daily intake of 400mcg for at least one month before and up to three months after conception. Pregnacare is designed for women of child-bearing age.

† Neural Tube Defects

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Nutritional Table

Wellman® Conception Nutritional Information	Av. per tablet	% NRV†
Siberian Ginseng Extract eq. to	30 mg	—
Peruvian Maca Extract eq. to	250 mg	—
Coenzyme Q10	2 mg	—
L-Carnitine	50 mg	—
Citrus Bioflavonoids	10 mg	—
L-Arginine	10 mg	—
Lycopene Extract	1.5 mg	—
Pine Bark Extract	30 mg	—
Octacosanol	3 mg	—
Inositol	40 mg	—
L-Glutathione	2.5 mg	—
Vitamin A (2500 IU)	750 µg RE	94
Vitamin D (as D3 600 IU)	15 µg	300
Vitamin E (Natural Source)	30 mg α-TE	250
Vitamin C	90 mg	113
Thiamin (Vitamin B1)	12 mg	1091
Riboflavin (Vitamin B2)	5 mg	357
Niacin (Vitamin B3)	18 mg NE	113
Vitamin B6	10 mg	714
Folic Acid	400 µg	200
Vitamin B12	75 µg	3000
Biotin	150 µg	300
Pantothenic Acid	10 mg	167
Magnesium	60 mg	16
Iron	6 mg	43
Zinc	15 mg	150
Copper	1000 µg	100
Manganese	0.5 mg	25
Selenium	150 µg	273
Chromium	50 µg	125

† NRV – Nutrient Reference Value, µg – microgram, mg – milligram, IU – International Units

Pregnacare® Conception Nutritional Information	Av. per tablet	% NRV†
Inositol	50 mg	—
N-Acetyl Cysteine	50 mg	—
Betacarotene (Natural Source)	3 mg	—
Coenzyme Q10	20 mg	—
Vitamin D (as D3 800 IU)	20 µg	400
Vitamin E (Natural Source)	4 mg α-TE	33
Vitamin C	90 mg	113
Thiamin (Vitamin B1)	8 mg	727
Riboflavin (Vitamin B2)	5 mg	357
Niacin (Vitamin B3)	20 mg NE	125
Vitamin B6	10 mg	714
Folic Acid	400 µg	200
Vitamin B12	20 µg	800
Biotin	150 µg	300
Pantothenic Acid	6 mg	100
Magnesium	60 mg	16
Iron	14 mg	100
Zinc	15 mg	150
Copper	1000 µg	100
Selenium	50 µg	91
Iodine	150 µg	100

DIRECTIONS

MEN - ONE TABLET PER DAY, WITH YOUR MAIN MEAL (PURPLE BLISTER).
WOMEN - ONE TABLET PER DAY, WITH YOUR MAIN MEAL (PINK BLISTER).

See side panel for more information about taking Pregnacare Conception.

Swallow with water or a cold drink. Not to be chewed. Do not exceed recommended intake. To be taken only on a full stomach.

- Suitable for vegetarians
- Free from artificial colours or preservatives
- No lactose, yeast or gelatin
- Pregnacare & Wellman are not tested on animals

Key Points

- Pregnacare Him & Her Conception is specifically designed to support men and women who are trying for a baby and concerned about their fertility.
- Unique scientifically based formulas from Vitabiotics to support fertility and reproductive health.
- Contains key specific ingredients including zinc, co-enzyme Q10, lycopene, inositol and folic acid to support conception.
- From Pregnacare, the UK's best selling and most trusted pregnancy supplement brand.
- Formulated by experts and independently approved by senior university nutritionists
- Contains the Chief Medical Officers' recommended amount of 400µg folic acid, essential before conception, plus vitamin B12.
- All ingredients included on the basis of well established, published research. Excessive levels of iron and other nutrients have been avoided, to protect the growing child.
- Drug free - 100% vitamin and mineral formula. Does not contain vitamin A.
- Fully licensed manufacture according to strict quality control.

Supporting References

Clinical Trial shows women taking prenatal micronutrient supplements have a higher chance of pregnancy

Conducted at University College London and The Royal Free Hospital

The results of a randomised controlled clinical trial published in the Reproductive BioMedicine Online (Friday 2nd December 2011) show that women having fertility treatment have significantly higher pregnancy rates when taking a specific conception micronutrient supplement formula (Pregnacare-Conception, Vitabiotics, London) compared with those taking folic acid alone.

Almost 70 percent (66.6 percent) of women became pregnant in the micronutrient group compared with under 40 percent (39.3 percent) of women in the folic acid group[1]. The ongoing pregnancy rate (confirmation of a viable pregnancy with a foetal heartbeat on ultrasound examination after 12 weeks of pregnancy) in women on the prenatal micronutrient supplement was 60 percent vs 25 percent[2] in the folic acid group.

The trial also showed that women taking the micronutrient supplement achieved pregnancy in significantly fewer attempts compared with women on folic acid alone.

This study is the first to demonstrate that prenatal micronutrient supplementation improves pregnancy rates in women with ovulation disorders and unexplained subfertility and who are undergoing standard ovulation induction treatment.

The study of fifty-eight women with fertility problems was carried out at University College London and The Royal Free Hospital, UK, a tertiary referral fertility centre. Women in this study were from good socioeconomic background and therefore were nutritionally adequate. Dietary records confirmed that both groups of women were on adequate balanced diets and that the dietary habits did not differ between the two groups of women.

The other main findings of the study included:

- Women who were on the prenatal micronutrient supplements took fewer treatment attempts to become pregnant.
- Three quarters of women (75 percent) conceived in their first attempt
- 20 percent of women conceived in their second attempt
- 5 percent of women conceived in their third attempt
- However in women taking folic acid[3] alone as an adjuvant to fertility treatment, the number of attempts needed to conceive was significantly higher:
- 18 percent of women conceived in their first attempt
- 18 percent of women conceived in their second attempt
- 64 percent of women conceived in their third attempt

Dr Rina Agrawal MD, MRCOG, PhD, the lead researcher commented, "The implications of this study are far reaching as they suggest that prenatal micronutrient supplementation in women undergoing ovulation induction improve pregnancy rates. This research further supports the fact that suboptimal nutrition is associated with significantly high reproductive risks such as difficulty in conceiving and a higher risk of miscarriages. All women considering pregnancy should take a specially formulated prenatal micronutrient supplement including folic acid and vitamin B12 such as Pregnacare-Conception (Vitabiotics, London) to optimise their chances of conception. There is a large body of evidence establishing the relationship between placental development, foetal growth, pregnancy outcomes and adequate nutrition, particularly vitamin intake. There is a need for

further awareness and education in this area as many women are still unaware of the importance of lifestyle changes, having a healthy diet and taking a prenatal micronutrient supplement pre-conceptually."

The beneficial effects of the micronutrient supplement (Pregnacare-Conception) may have been mediated not only through multiple vitamins and minerals but through its essential constituents of antioxidants such as vitamin C, zinc and n-acetyl cysteine and insulin sensitisation with inositol.

Based on the results of this study, a larger follow-up study is already underway.

Periconceptional supplementation of micronutrients, particularly folic acid, vitamin B6, vitamin C, vitamin D, vitamin E, iodine, selenium, iron and DHA may have a positive impact on infertility treatment.

A 2013 meta-analysis of the current evidence supporting the supplementation of certain nutrients to support fertility concluded that the nutrients most strongly linked to improved fertility characteristics in women were folic acid, vitamin B6, vitamin C, vitamin D, vitamin E, iodine, selenium, iron and DHA.

Reference: The effect of micronutrient supplements on female fertility. *Kai J. Buhling and Donata Grajecki, Curr Opin Obstet Gynecol, 2013, 25:173-180.*

Preconception multivitamin use linked to better pregnancy outcomes

A study has found that women who took multimicronutrients (multivitamins) were 19% less likely to have a low birth weight baby. When compared with women taking iron and folic acid only, the researchers found the multimicronutrient users had a 17% lower risk of having a low birth weight baby. *(CMAJ, June 9, 2009)*

A large Danish study has found that regular multivitamin use during the preconception period is associated with a reduced risk of preterm births (PTBs) or small-for-gestational-age (SGA) births.

Some 35,897 Danish women were assessed for relationship between multivitamin use during a 12-wk preconceptional period and risk of SGA births and PTBs.

Multivitamin use was associated with reduced risks of a PTB and preterm labour however only in women with a healthy weight BMI (<25). Risk reduction was stronger in women who reported longer use of multivitamins compared to women who reported only partial use.

Comment: This finding adds to evidence suggesting that women who are using multivitamins at the time of conception may have better pregnancy outcomes, similar to those seen with folic acid supplementation.

Reviewed by Benjamin Brown ND

Clinical Trial shows high prevalence of vitamin D insufficiency in early pregnancy, maternal vitamin D supplementation of 20µg/d is advisable to maintain maternal vitamin D status in pregnant women.

Based on an original study on Pregnacare conducted by Dr Mary McCann, School of Biomedical Sciences, Ulster University, 2019.

Alhomaid, R., Mulhern, M., Cassidy, L., Laird, E., Healy, M., Strain, S., Livingstone MBE, Parker MJ & McCann, M. (2020). Effect of vitamin D supplementation on vitamin D status in pregnant women: Findings from the MO-VITD study. *Proceedings of the Nutrition Society, 79*(OCE2), E99. doi:10.1017/S0029665120000476

Alhomaid, R., Mulhern, M., Cassidy, L., Laird, E., Healy, M., Strain, S., Livingstone, B., Parker, M., &. McCann, M. (2020). The association between maternal body weight and vitamin D status in early pregnancy: Findings from the MO-VITD study. *Proceedings of the Nutrition Society, 79*(OCE2), E586. doi:10.1017/S0029665120005352

Alhomaid, R., Mulhern, M., Cassidy, L., Laird, E., Healy, M., Strain, S., Livingstone MBE, Parker MJ & McCann, M. Maternal Obesity and baseline vitamin D insufficiency alter the response to vitamin D supplementation (Am J Clin Nutr 2021;0:1–11.2021).

A double-blind randomised vitamin D intervention study to assess the effect of supplementation of 10µg vs 20µg vitamin D throughout pregnancy on vitamin D status of normal weight, overweight and obese pregnant women and on the vitamin D status of cord blood of their infants**.** The subjects were 240 pregnant women in Northern Ireland, with equal numbers in each BMI category**.** Pregnant women assigned to receive 10µg or 20µg vitamin D from 12 weeks gestations until delivery

Key findings:

- Women who **started pregnancy with insufficient** 25(OH)D concentrations **remained insufficient** throughout pregnancy in the **10µg/d group** (49.9±28.2nmol/L at trimester 3)
- In the **20µg/d group**, women **starting pregnancy as insufficient achieved levels of sufficiency in the 2nd**(58.9±30.6nmol/L) **and 3rd** (64.0±35.9nmol/L) **trimesters**
- Women who **started pregnancy with sufficient** vitamin D status (25(OH)D>50nmol/L), **maintained levels of sufficiency throughout pregnancy irrespective of treatment group** (83.1±24.4 and 96.7±30.7 at trimester 3 in 10µg/d and 20 µg/d groups respectively)

Based on the findings of the **high prevalence of vitamin D insufficiency in early pregnancy, maternal vitamin D supplementation of 20µg/d is advisable** to maintain maternal vitamin D status in pregnant women.

References:

Catov JM, Bodnar LM, Olsen J, et al. Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort. Am J Clin Nutr. 2011 Sep;94(3):906-12.

'Fertility, conception, implantation, fetal organogenesis and placentation are the critical stages potentially affected by nutrition during the periconceptional period.

The preconceptional period is particularly important since it affects both fertility and the early stages of gestation.

The overall data indicates that micronutrients may affect fertility, embryogenesis and placentation, and the prophylactic use of some micronutrients may be useful in preventing several adverse pregnancy outcomes.

In particular, diet during the first trimester may be more important to development and differentiation of various organs. Moreover, also preconceptional nutrition is crucial for an optimal onset and development of pregnancy. Unfortunately, nutritional intake of childbearing-age women appears to be inadequate during the preconceptional period (de Weerd et al., 2003b; Mouratidou mainly in terms of micronutrients, but also considering the global shift towards the Western diet.'

'Role of micronutrients in the periconceptional period', Human Reproduction Update, Cetin I, Berti C, Calabrese S, 2010;16seleniu

Maternal MMN had long-term benefits for child cognitive development at 9–12 years of age, thereby supporting its role in early childhood development, and policy change toward MMN.

Children of mothers given MMN had a mean score of 0·11 SD (95% CI 0·01–0·20, p=0·0319) higher in procedural memory than those given IFA, equivalent to the increase in scores with half a year of schooling. Children of anaemic mothers in the MMN group scored 0·18 SD (0·06–0·31, p=0·0047) higher in general intellectual ability, similar to the increase with 1 year of schooling.

'Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial', The Lancet Global Health, Vol 5, No 2, Feb 2017A significantly higher rate of conceptions occurred after preconCeptional multivitamin supplementation in comparison with a placebo – like trace element supplementation in a randomised, double-blind, controlled trial (Czeizel A.E. Et Al 1996 Int J Vitam Nutr Res; 66 (1): 55-8)

"Periconceptual multivitamin supplementation can reduce not only the rate of neural tube defects, but also the rate of other

major non-genetic syndromatic congenital abnormalities." *(A.E. Czeizel, BMJ 1993; 306 1645-8)*

Moderate food restriction during pregnancy produces intrauterine growth retardation, and results in newborns with low trace element contents (particularly in copper), which make them dependent on correct postnatal supply. *(M.P. Vaquero, et al, Reprod Nutr Dev 1996;36(3):333-44)*

In a double-blind placebo controlled randomised trial of periconceptional supplementation of folic acid with multivitamins and trace elements in Hungary, a significant prevention of the first occurrence of neural tube defect, urinary tract and cardiovascular defects, and a decrease in the rate of limb deficiencies and congenital hypertrophic pyloric stenosis was found. Supplementation could also reduce the occurrence of nausea and vomiting. *(A.E. Czeizel, Eur J Obstet Gynecol Reprod Biol 1998 Jun;78(2):151-61)*

Women of reproductive age should be advised to take multivitamin supplements containing 400 mcg folic acid daily. *(G.J. Locksmith, et al, Obstet Gynecol 1998 Jun;91(6):1027-34)*

In a case-control study across North America, Europe and Israel including 1,051 mothers of children with primary pediatric brain tumors and 1,919 controls, combined results suggested that maternal vitamin supplementation decreased risk of brain tumor. There was a trend of less risk with longer duration of use (risk lowest for supplement use during all 3 trimesters). *(S. Preston-Martin, et al, Int J Cancer Suppl 1998;11:17-22)*

In the United States, prenatal vitamins are commonly prescribed during pregnancy. *(R.V. Acuff, et al, Am J Clin Nutr 1998;67:459-64)*

In a cross-sectional study of 60 lactating and 41 non-lactating postpartum women, and 13 nulliparous women, results suggests that nutritional factors such as maternal iron status and use of dietary supplements play a role in a mother's postpartum immune status. *(J.P. Zimmer, et al, Am J Clin Nutr 1998 May; 67(5):897-904)*

In a study on the effects of vitamin supplements on the nutritional content of milk at six months postpartum in 6 women fed a well-balanced diet compared to 6 similar women who did not take supplements, supplementation did not significantly affect milk concentrations of vitamins B6, B12, B1, B2, vitamin C or folate. *(M.R. Thomas, et al, Am J Clin Nutr 1980 Oct;33(10):2151-6)*

Maternal folate status is an important determinant of infant birth weight.(Relton CL, Pearce MS, Parker L. 2005. The influence of erythrocyte folate and serum vitamin B12 status on birth weight. *Br J Nutr*. **93**(5):593-9).

In a review of 55 medical papers published from 1990 through to 1997, the majority of evidence demonstrates a decreased incidence of neural tube defects with increased folic acid consumption. The most convincing trials were performed in Europe among women who were planning pregnancy by using multivitamin or folic acid supplements. *(G.J. Locksmith, et al, Obstet Gynecol 1998 Jun;91(6):1027-34)*

In a study of 45,300 children, it was found that maternal exposure to folic acid and multivitamin supplements before and during pregnancy is associated with a reduced risk of ASD in the offspring, compared with the offspring of mothers without such exposure. (S. Levine, et al, JAMA Psychiatry, 2018 January 3, doi:10.1001/jamapsychiatry.2017.4050; Association of Maternal Use of Folic Acid and Multivitamin Supplements in the Periods Before and During Pregnancy With the Risk of Autism Spectrum Disorder in Offspring)

Coenzyme Q10

A total of 169 participants were evaluated (76 treated with CoQ10 and 93 controls); 17 women were excluded due to low compliance with CoQ10 administration. The baseline demographic and clinical characteristics were comparable between the

groups. Pretreatment with CoQ10 improves ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles. (*Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod Biol Endocrinol. 2018;16(1):29. Published 2018 Mar 27. doi:10.1186/s12958-018-0343-0*)

Fifteen female partners of infertile couples, aged 31–46, undergoing IVF-ET and taking 200 mg/day oral CoQ10 were compared to unsupplemented patients. CoQ10 content, its oxidative status and total antioxidant capacity were evaluated also in relation to oocyte maturation indexes. Our observation leads to the hypothesis that the oral supplementation of CoQ10 may improve follicular fluid oxidative metabolism and oocyte quality, specially in over 35-year-old women. (*Giannubilo SR, Orlando P, Silvestri S, Cirilli I, Marcheggiani F, Ciavattini A, Tiano L. CoQ10 Supplementation in Patients Undergoing IVF-ET: The Relationship with Follicular Fluid Content and Oocyte Maturity. Antioxidants. 2018; 7(10):141*).

The objective of this study is to compare the combination of dehydroepiandrosterone (DHEA) and coenzyme Q10 (CoQ10) (D + C) with DHEA alone (D) in intrauterine insemination (IUI) and *in vitro* fertilization (IVF) cycles among patients with decreased ovarian reserve. D + C significantly increases AFC and improves ovarian responsiveness during IUI and IVF without a difference in clinical outcome. (*Itai Gat, Sonia Blanco Mejia, Hanna Balakier, Clifford L. Librach, Anne Claessens & Edward A.J. Ryan (2016) The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve, Gynecological Endocrinology, 32:7, 534-537*).

Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. (*Teran E, Hernandez I, Nieto B, Tavara R, Ocampo JE, Calle A. Int J Gynaecol Obstet. 2009 Apr;105(1):43-5. doi: 10.1016/j.ijgo.2008.11.033. Epub 2009 Jan 19)*

Coenzyme Q10 and alpha-tocopherol are potent antioxidants, and the decreased levels of these two antioxidants in preeclampsia may alter the normal redox balance, thereby reducing the ability of antioxidant defenses to protect against free radical damage. This could be a factor in the endothelial cell damage observed in preeclampsia. (*Lipid-soluble antioxidants and pregnancy: maternal serum levels of coenzyme Q10, alpha-tocopherol and gamma-tocopherol in preeclampsia and normal pregnancy. Palan PR, Shaban DW, Martino T, Mikhail MS. Gynecol Obstet Invest. 2004;58(1):8-13. Epub 2004 Feb 25).*

The fundamental role of coenzyme Q(10) (CoQ(10)) in mitochondrial bioenergetics and its well-acknowledged antioxidant properties constitute the basis for its clinical applications, although some of its effects may be related to a gene induction mechanism. Cardiovascular disease is still the main field of study and the latest findings confirm a role of CoQ(10) in improving endothelial function. The possible relation between CoQ(10) deficiency and statin side effects is highly debated, particularly the key issue of whether CoQ(10) supplementation counteracts statin myalgias. Furthermore, in cardiac patients, plasma CoQ(10) was found to be an independent predictor of mortality. Studies on CoQ(10) and physical exercise have confirmed its effect in improving subjective fatigue sensation and physical performance and in opposing exercise-related damage. In the field of mitochondrial myopathies, primary CoQ(10) deficiencies have been identified, involving different genes of the CoQ(10) biosynthetic pathway; some of these conditions were found to be highly responsive to CoQ(10) administration. The initial observations of CoQ(10) effects in Parkinson's and Huntington's diseases have been extended to Friedreich's ataxia, where CoQ(10) and other quinones have been tested. CoQ(10) is presently being used in a large phase III trial in Parkinson's disease. CoQ(10) has been found to improve sperm count and motility on asthenozoospermia. Moreover, for the first time CoQ(10) was found to decrease the incidence of preeclampsia in pregnancy. The ability of CoQ(10) to mitigate headache symptoms in adults was also verified in pediatric and adolescent populations. (*Littarru GP1, Tiano L.Nutrition. Clinical aspects of coenzyme Q10: an update. 2010 Mar;26(3):250-4. doi: 10.1016/j.nut.2009.08.008. Epub 2009 Nov 22*).

Studies have shown that low blood CoQ10 levels are associated with an increased risk of pre-eclampsia (*Palan, P. R., Shaban, D. W., Martino, T., & Mikhail, M. S. (2004). Lipid-soluble antioxidants and pregnancy: maternal serum levels of coenzyme Q10, alpha-tocopherol and gamma-tocopherol in preeclampsia and normal pregnancy. Gynecologic and Obstetric Investigation, 58(1), 8–13*).

Studies have shown that low blood CoQ10 levels are associated with an increased risk of miscarriage (*Noia, G., Littarru, G. P., De Santis, M., Oradei, A., Mactromarino, C., Trivellini, C., & Caruso, A. (1996). Coenzyme Q10 in pregnancy. Fetal Diagnosis and Therapy, 11(4), 264–270*).

Coenzyme Q10 plays a crucial role in improving endothelial function. CoQ10 has a hypotensive effect (*Littarru, G. P., Tiano, L., Belardinelli, R., & Watts, G. F. (2011). Coenzyme Q10 , endothelial function, and cardiovascular disease. Biofactors (Oxford,*

England), 37(5), 366–373).

The best study we have to date – a randomized controlled study – enrolled 235 pregnant women. 118 women were randomly assigned to take 200 milligrams of CoQ10 daily from week 20 of the pregnancy until delivery. 117 women were assigned to take a matching placebo for the same period. Only 17 women in the CoQ10 treatment group developed pre-eclampsia compared with 30 women in the placebo group. The 43% reduction in the risk of developing pre-eclampsia was statistically significant. The researchers concluded that daily supplementation with CoQ10 reduces the risk of developing pre-eclampsia. There were no adverse effects of taking 200 milligrams of CoQ10 from week 20 of the pregnancy until delivery, neither for the mother nor for the baby *(Teran, E., Hernandez, I., Nieto, B., Tavara, R., Ocampo, J. E., & Calle, A. (2009). Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. International Journal of Gynaecology And Obstetrics, 105(1), 43–45).*

Teran et al reported that in pregnant women with pre- eclampsia there is a significant decrease in plasma levels of CoQ10 compared with normal pregnant women. (*Teran E, Racines-Orbe M, Vivero S, Escudero C, Molina G, Calle A. Pre-eclampsia is associated with a decrease in plasma coenzyme Q10 levels. Free Radic Biol Med. 2003;35:1453-1456*).

Roland et al determined the plasma levels of CoQ10, vitamin E, thromboxane, and prostacyclin in normotensive and pre-eclamptic pregnant women and concluded that CoQ10 is a sensitive marker of oxidative stress in pre-eclampsia. (*Roland L, Gagne A, Belanger MC, et al. Existence of compensatory defense mechanisms against oxidative stress and hyperten- sion in pre-eclampsia. Hypertens Pregnancy. 2010;29:21-37*).

Inositol

Women with oligomenorrhea and polycystic ovaries show a high incidence of ovulation failure and reports have shown that inositol may help ovarian function. The aim of the study was to use a double blind, placebo controlled approach with detailed assessment of ovarian activity to assess the validity of this therapeutic approach in this group of women. The results showed that ovulation frequency was significantly higher in the treated group compared with the placebo, therefore the data supports a **beneficial effect of inositol in improving ovarian function in women with oligomenorrhea and polycystic ovaries**. (Gerli S. et al 2003 Eur Rev Med Pharmacol Sci Nov-Dec;7(6):151-9)

D-chiro-inositol offers a safe and effective method for preventing folic acid-resistant NTDs in the curly tail mouse. This raises the possibility of using inositol as an adjunct therapy to folic acid for prevention of Neural Tube Defects (NTDs) in humans. (Cogram, P. *et al*: Human Reproduction, Vol. 17, No. 9, 2451-2458, September 2002)

Inositol is involved in several aspects of reproduction. It affects overall embryogenisis and may help prevent neural tube defects**.. Inositol concentrations in male and female reproductive organs are several times higher than else where**, suggesting it plays a role in human reproduction. This is confirmed by the role of inositol in normal (early) embryonic growth in several animal species.(Beemster P. *et al* March 2002: Nutrition Reviews, vol 60, No 3, 80-87)

The authors investigated the administration of an isoform of inositol (myo-inositol), belonging to the vitamin B complex, to see if it would improve the insulin-receptor activity, restoring normal ovulatory function. Twenty-five PCOS women of childbearing age with oligo- or amenorrhea were enrolled in the study. Twenty-two out of the 25 (88%) patients restored at least one spontaneous menstrual cycle during treatment, of whom 18 (72%) maintained normal ovulatory activity during the follow-up period. A total of 10 singleton pregnancies (40% of patients) were obtained. Nine clinical pregnancies were assessed with fetal heart beat at ultrasound scan. It was therefore concluded that Myo-inositol is a simple and safe treatment that is capable of restoring spontaneous ovarian activity and consequently fertility in most patients with PCOS. (Papaleo E et al. Gynecol Endocrinol. 2007 Dec;23(12):700-3)

N-acetyl cysteine

The authors compared clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for inducing ovulation in patients with polycystic ovary syndrome. Results showed that ovulation rate improved significantly after the addition of N-acetyl cysteine (17.9% versus 52.1%). It was concluded that **N-Acetyl cysteine is proved effective in inducing or augmenting ovulation in polycystic ovary patients**. (Badawy A et al Acta Obstet Gynecol Scand. 2007;86(2):218-22)

The authors evaluated the effect of N-acetyl-cysteine (NAC), as an adjuvant therapy in subjects with polycystic ovary syndrome (PCOS) resistant to clomiphene citrate (CC). A placebo-controlled, double-blind randomized trial of one hundred fifty women diagnosed with CC-resistant PCOS, aged 18-39 years undergoing therapy for infertility were included.The results showed that a combination of CC and NAC significantly increased both ovulation rate and PR in women with CC-resistant PCOS (49.3% vs. 1.3% and 21.3% vs. 0%, respectively). The NAC as an adjuvant to CC was more effective than placebo for CC-resistant patients with PCOS. It is safe and well tolerated. (Rizk AY. Fertil Steril. 2005 Feb;83(2):367-70)

An appropriate local environment is necessary for successful implantation. Oxidative stress is implicated in the pathogenesis of several pathologies, and may contribute to early pregnancy failure. Antioxidant therapies have been studied in infertility. In this study, the authors have assessed the antioxidant activity of N-acetylcysteine (NAC), flavonoids (quercetin, catechin) and alpha-tocopherol in an oxidative model of endometrial cells (RL95). The antioxidant effect of NAC was better than that of quercetin. When catechin or alpha-tocopherol were used in the same conditions, no antioxidant effect was detected in cells in culture. These results demonstrate that NAC and quercetin are good H2O2 scavengers (Estany S et al. J Reprod Immunol. 2007 Aug;75(1):1-10)

Folic Acid (400µg)

The Department of Health's Chief Medical Officer recommends that women planning a pregnancy should take a supplement containing **400µg (0.4mg) folic acid** daily, from the start of trying to conceive until the 12th week of pregnancy. Folic acid when taken around the time of conception is vital to help prevent neural tube defects such as spina bifida. In the UK, 2000 pregnancies a year are affected by neural tube defects.

Folic acid should be taken for 6-12 months before pregnancy to build a mothers store. New studies are showing that as well as preventing neural tube defects, taking folic acid before pregnancy can cut the risk of premature births by 70%. The researchers included nearly 40,000 women and found that those who took a folic acid supplement for at least a year prior to becoming pregnant reduced their risk of preterm delivery between 20 and 28 weeks of gestation by 70 percent. A year of folic acid supplementation dropped the risk of delivering during weeks 28 through 32 by 50 percent, according to the study. *(Bukowski R, et al. (2009) PLoS Med 6(5): e1000061)*

Importance Prenatal folic acid supplements reduce the risk of neural tube defects in children, but it has not been determined whether they protect against other neurodevelopmental disorders.

Objective To examine the association between maternal use of prenatal folic acid supplements and subsequent risk of autism spectrum disorders (ASDs) (autistic disorder, Asperger syndrome, pervasive developmental disorder–not otherwise specified [PDD-NOS]) in children.

Design, Setting, and Patients The study sample of 85 176 children was derived from the population-based, prospective Norwegian Mother and Child Cohort Study (MoBa). The children were born in 2002-2008; by the end of follow-up on March 31, 2012, the age range was 3.3 through 10.2 years (mean, 6.4 years). The exposure of primary interest was use of folic acid from 4 weeks before to 8 weeks after the start of pregnancy, defined as the first day of the last menstrual period before conception. Relative risks of ASDs were estimated by odds ratios (ORs) with 95% CIs in a logistic regression analysis. Analyses were adjusted for maternal education level, year of birth, and parity.

Main Outcome Measure Specialist-confirmed diagnosis of ASDs.

Results At the end of follow-up, 270 children in the study sample had been diagnosed with ASDs: 114 with autistic disorder, 56 with Asperger syndrome, and 100 with PDD-NOS. In children whose mothers took folic acid, 0.10% (64/61 042) had autistic disorder, compared with 0.21% (50/24 134) in those unexposed to folic acid.

The adjusted OR for autistic disorder in children of folic acid users was 0.61 (95% CI, 0.41-0.90). No association was found with Asperger syndrome or PDD-NOS, but power was limited. Similar analyses for prenatal fish oil supplements showed no such association with autistic disorder, even though fish oil use was associated with the same maternal characteristics as folic acid use.

Conclusions and Relevance Use of prenatal folic acid supplements around the time of conception was associated with a lower risk of autistic disorder in the MoBa cohort. Although these findings cannot establish causality, they do support prenatal folic acid supplementation.

(Maternal Folic Acid Supplements and Autism.. American Medical Association, February 13, 2013—Vol 309, No. 6)

Another study involving 832 pregnancies in 1996 at the University of Medicine and Dentistry of New Jersey showed that women consuming less than 240mcg of folic acid per day had about two to three times greater risk of premature delivery and low infant birth weight. (*Scholl TO, et al. Am J Clin Nutr. 1996 Apr;63(4):520-5.)*

Higher maternal folate coupled with vitamin B12 insufficiency was associated with higher GDM risk. This finding has potential implications for antenatal supplement recommendations. *(S Lai et al., 2018, Journal of Clinical Nutrition, 37:3)*

Diet alone cannot provide enough folic acid

Women can expect to receive around 200 micrograms of folic acid in a normal balanced diet, but before and during pregnancy an additional 400 micrograms is recommended. To reach this amount without a supplement would require the equivalent of an extra 7 servings of broccoli daily, on top of the average diet. As this is not a realistic proposition, all women planning a pregnancy are advised to increase their intake of folate-rich foods and take a 400mcg supplement.

Research published in The Lancet also shows that women who used multivitamins containing folic acid, had a 25 - 50% reduction in risk of having babies with Cleft palates, compared to women who did not use vitamins. The risk of Cleft palate, the most common congenital abnormality, was reduced if the supplement was taken one month before, through to two months after conception.

To prevent first occurrence of NTD, the Department of Health recommends that all women who could become pregnant should take 400µg **folic acid** per day as a medicinal or food supplement prior to conception until the twelfth week of pregnancy (DH, 1992). To prevent recurrence of NTD in the offspring of women or men with spina bifida themselves, or with a history of a previous child with an NTD, a dose of 5mg/day is advised. Diabetes UK also recommends that all women with diabetes should take 5mg/day before conception and during the first 12 weeks of pregnancy.' *'Folate And Disease Prevention', Scientific Advisory Committee on Nutrition, 2006, page 31.*

Pregnant women usually meet their increased energy needs but do not always meet their increased micronutrient requirements. The supply of both **folic acid** and **docosahexaenoic acid** (DHA) has been related to positive pregnancy and infant outcomes.'(*The American Journal of Clinical Nutrition, Krauss-Etschman S, Shadid R, Campoy C, et al, 2007;8)*

Folic acid fortification is associated with significant decreases in the prevalence of spina bifida. (*Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. 2005. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics, 116(3), 580-6).*

Botto LD, Lisi A, Robert-Gnansia E, Erickson JD, Vollset SE, Mastroiacovo P, Botting B, Cochi G, de Vigan C, de Walle H, Feijoo M, Irgens LM, McDonnell B, Merlob P, Ritvanen A, Scarano G, Siffel C, Metneki J, Stoll C, Smithells R, Goujard J. 2005. International retrospective cohort study of neural tube defects in relation to folic Acid recommendations: are the recommendations working? *Obstet Gynecol Surv,* 60(9), 563-5

Mahadevan B, Bhat BV. 2005. Neural tube defects in Pondicherry. *Indian J Pediatr;* 72(7), 557-9.

Byrne J, Carolan S, Arcement R, Kozlowski M, Taller I, Ried S, Keating R. 2005. An intervention study to increase knowledge and use of folic acid among relatives in neural tube defect-affected families in Washington, D.C. *Birth Defects Res A Clin Mol Teratol*, 73(6): 424-9.

Lopez-Camelo JS, Orioli IM, da Graca Dutra M, Nazer-Herrera J, Rivera N, Ojeda ME, Canessa A, Wettig E, Fontannaz AM, Mellado C, Castilla EE. 2005. Reduction of birth prevalence rates of neural tube defects after folic acid fortification in Chile. *Am J Med Genet A,* 135(2): 120-5.

Folic acid food fortification is associated with a pronounced reduction in open neural tube defects.(*Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DE. 2002.Association of neural tube defects and folic acid food fortification in Canada. Lancet,* ***360****(9350):2047-*8.)

Ahluwalia IB, Daniel KL. 2001. Are women with recent live births aware of the benefits of folic acid? MMWR Recomm Rep, 50(RR-6): 3-14.

Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, Sutton LN, Whitehead AS. 2004. Spina bifida. *Lancet.* 364(9448): 1885-95.

Regardless of dieting status, public health programs should stress the importance of women in their childbearing years consuming 400 micro g of folic acid daily through supplements, fortified foods, and a diet containing folate-rich foods.*(Centers for Disease Control and Prevention (CDC). 2004. Use of vitamins containing folic acid among women of childbearing age--United States. MMWR Morb Mortal Wkly Rep. 53(36), 847-50.*

Simmons CJ, Mosley BS, Fulton-Bond CA, Hobbs CA. 2004. Birth defects in Arkansas: is folic acid fortification making a difference? *Birth Defects Res A Clin Mol Teratol,* 70(9), 559-64.

Clinically, many naturopathic and other doctors recommend the use of vitamin B complex 50 mg per day with additional folic acid to try to prevent miscarriage (also known as spontaneous abortion). These practices for prevention of spontaneous abortion are supported by some studies suggesting a connection between impaired homocysteine metabolism and recurrent miscarriages *(Del Bianco A, Maruotti G, Fulgieri AM, Celeste T, Lombardi L, Amato NA, Pietropaolo F. 2004. Recurrent spontaneous miscarriages and hyperhomocysteinemia. Minerva Ginecol, 56(5), 379-83)*

Kumar KS, Govindaiah V, Naushad SE, Devi RR, Jyothy A. 2003. Plasma homocysteine levels correlated to interactions between folate status and methylene tetrahydrofolate reductase gene mutation in women with unexplained recurrent pregnancy loss. J Obstet Gynaecol, 23(1): 55-8.

An important factor in the prevention of spina bifida. The UK department of health now recommends "a supplement containing 400mcg Folic Acid both during pregnancy and from when they begin to try to conceive."
(MRC Multivitamin Study Research Group. Prevention of neural tube defects: Results of the MRC Vitamin Study. Lancet 1991;338:131-7)

Folic acid is an important factor in the prevention of spina bifida. The UK department of health now recommends "a supplement containing 400mcg Folic Acid both during pregnancy and from when they begin to try to conceive." *(UK Department of Health; Health Publication Unit. Folic acid and the prevention of neural tube defects.. Lancet 1993; 341:46). (Dr Kenneth Calman, Government Chief Medical Officer)*

Folate functions in multiple coenzyme forms in acceptance, redox processing and transfer of one-carbon units, including nucleotides and certain amino acids. *(L.B. Bailey, et al, J Nutr 1999 Apr;129(4):779-82)*

In a study of 33 women with normal pregnancies and 21 women with preeclampsia, the mean total plasma homocysteine in preeclamptic women was significantly higher than in controls. Despite no indications of overt folate deficiency, high homocysteine levels were weakly correlated with low plasma folate concentrations. *(R.W. Powers, e tal, Am J Obstet Gynecol*

1998 Dec;179(6 Pt 1):1605-11)

The Public Health Service in the United States recommends that all women capable of childbearing consume 400 mcg folic acid per day to decrease the risk of having a pregnancy affected by a neural tube defect. *(M.L. Neuhouser, et al, J Am Coll Nutr 1998 Dec;17(6):625-30)*

95% of cases of spina-bifida occur in babies born to women without a known family history of this type of disorder. The idea that dietary measures alone [i.e. without supplements] may suffice to ensure effective prevention is invalid. *(R. Bradai, et al, Contracept Fertil Sex 1999 Mar;27(3):238-42)*

Both observational and controlled intervention trials have shown periconceptional folic acid supplementation to significantly reduce the incidence both of first-time and recurrent neural tube defects, and possibly to reduce the incidence of other congenital malformations, preterm delivery, and intra-uterine growth retardation. *(R. Kihlberg, et al, Lakartidningen 1999 Apr 21;96(16):1961-3)*

Implementation of a national strategy to reduce the incidence of neural tube defects and promote awareness of the benefits of periconceptional folic acid supplementation is strongly to be recommended. *(R. Kihlberg, et al, Lakartidningen 1999 Apr 21;96(16):1961-3)*

Studies provide unambiguous evidence that the occurrence and recurrence of pregnancies complicated by neural tube malformations were reduced by folic acid supplementation at the time of conception. *(S.P. Rothenberg, et al, Semin Hematol 1999 Jan;36(1):65-74)*

High levels of plasma homocysteine have been found in women who gave birth to offspring with neural tube defects and other birth defects. Elevated homocysteine levels can be explained by lack of B vitamins and folic acid. *(T.K. Eskes, Nutr Rev 1998 Aug;56(8):236-44)*

The incidence of neural tube defects including myelomeningocele, which is one the most common causes of infant and childhood disability, can be substantially reduced by folic acid supplementation to women before and during the early stages of pregnancy. *(J.D. Morrow, et al, J Pediatr Health Care 1998 Mar-Apr;12(2):55-9)*

Even in large dose (20 mg daily) folic acid has never been shown to harm normal people. *(C.J. Dickinson, QJM 1995 May;88(5):357-64)*

In a study of 194,946 children, it was found that the risk of autism was “significantly lower” for those children exposed to anti-epileptic drugs in utero where the mother had taken folic acid supplements. The study concluded that those mothers who are using anti-epileptic drugs should take folic acid supplements continuously. (*M. Bjork, et al, JAMA Neurol, 2017 December 26*, *doi:10.1001/jamaneurol.2017.3897; Association of Folic Acid Supplementation During Pregnancy With the Risk of Autistic Traits in Children Exposed to Antiepileptic Drugs In Utero)*

First randomized trial evidence shows that continued folic acid supplementation of mothers through the second and third trimesters of pregnancy can influence the cognitive performance of their children up to 7 years of age. The results show that there are benefits for the child of continuing maternal use of folic acid throughout pregnancy, whereas current recommendations in most countries worldwide advise mothers to take folic acid supplements from before conceiving until the end of the 12th gestational week only. At 3 years, children born to women who took folic acid throughout pregnancy showed significantly higher cognition scores and at 7 years significantly better word reasoning compared with placebo. At both ages, greater proportions of children of the folic acid group had cognitive scores above the scales’ median values compared with placebo. Compared with a representative sample of British children at 7 years of age, WPPSI-III scores were higher in children of the folic acid group for general language as well as verbal, performance and full scale IQ. The placebo group showed smaller differences than the folic acid arm for verbal and full scale IQ, but still higher than the national sample, and no differences for performance IQ or general language (*McNulty, H., Rollins, M., Cassidy, T. et al. Effect of continued folic acid supplementation beyond the first*

trimester of pregnancy on cognitive performance in the child: a follow-up study from a randomized controlled trial (FASSTT Offspring Trial). BMC Med 17, 196 (2019) doi:10.1186/s12916-019-1432-4).

Folate is required for deoxyribonucleic acid (DNA) synthesis and normal cell division, production of erythrocytes and formation of the monoamine neurotransmitters (eg serotonin). (*Sadler TW. American Journal of Medical Genetics Part C:Seminars in Medical Genetics. 2005;135C:2-8. Mahmood L. Journal of Health Research and Reviews. 2014;1:5-9. Miller AL. Alternative Medicine Review. 2008;13:216-26)*

Folate is part of a biological cycle that converts the amino acid homocysteine into methionine. Therefore, poor folate supply leads to higher plasma homocysteine concentrations, which seems to be associated with an increased risk of placental abruption, intrauterine growth restriction, pre-eclampsia, pregnancy loss, still birth and clubfoot. (*Chaudhry SH, et al. BMC Pregnancy and Childbirth. 2019;19:75. Allen LH. The American Journal of Clinical Nutrition 2005;81:1206s-1212s*)

Vitamin B12

The authors describe an oligomenorrheic infertile patient with evidence of vitamin B12 deficiency. A treatment programme was created, including oestrogen and hCG and pregnancy occurred after 1,000 micrograms of Vitamn B12 was added to the treatment regimen. There is therefore evidence that a B12 deficiency can cause failure to ovulate. (Sanfilippo JS and Liu YK 1991 Int J Fertil; 36(1):36-8)

The authors examined the relationship of infertility to recurrent foetal loss in patients who were vitamin B12 deficient. The authors concluded that when vitamin B12 deficiency develops, hypercoagulability due to raised homocysteine levels may lead to foetal loss. A more prolonged deficiency results in infertility by causing changes in ovulation or development of the ovum or changes leading to defective implantation. (Bennet M. J Reprod Med. 2001 Mar;46(3):209-12)

Vitamin B 12 deficiency can be responsible for intracellular folate cycle failure. (Candito M, Houcher B, Boisson C, Abellard J, Demarcq MJ, Gueant JL, Benhacine K, Gerard P, Van Obberghen E. 2004. *Ann Biol Clin,* 62(2), 235-8)

Suarez L, Hendricks K, Felkner M, Gunter E. 2003. Maternal serum B12 levels and risk for neural tube defects in a Texas-Mexico border population. Ann Epidemiol, 13(2): 81-8.

Low Vitamin B (12) level as a risk factor for very early recurrent abortion (Eur J Obstet Gynecol Reprod Biol. 2002 Sep 10;104(2):156-9)

Haematinic nutrient essential for the formation of haemoglobin, for the red blood cells of both mother and growing child.

A study involving 56,000 women by Trinity College , Dublin which was published in the Quarterly Journal of Medicine showed there was convincing evidence that low levels of vitamin B12, as well as folic acid, resulted in babies being born with nervous system abnormalities. *(Maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects. Quarterly Journal of Medicine 1993; 86 : 703-708)*

All evidence shows that women contemplating pregnancy should be taking folic acid and vitamin B12. *(The Times Nov.25, 1993)*

In a study of 16 women with neural tube defects pregnancies and 64 age-matched controls, the amniotic fluid from the neural tube defect pregnancies had lower vitamin B12 concentrations. *(M.T. Steen, et al, Prenat Diagn 1998 Jun; 18(6):545-55)*

The human placenta modulates the asymmetric transfer of vitamin B12 on the basis of release of specific cobalamin-binding proteins into the maternal and fetal perfusates. *(R.E. Perez-D'Gregorio, et al, J Pediatr 1998 Mar;132(3 Pt 2):S35-42)*

Lack of vitamin B12 in the maternal diet during pregnancy has been shown to cause severe retardation of myelination in the nervous system, as seen in the case of a child of strictly vegetarian parents who presented with severe psychomotor retardation. *(K. Lovblad, et al, Pediatr Radiol 1997 Feb;27(2):155-8)*

Significant differences in fetal vitamin B12 status were found between between pregnancies with anencephaly and spina bifida, as well as between anencephaly cases and controls. *(B. Thorand, et al, Z Geburtshilfe Neonatol 1996 Sep-Oct;200(5):176-80)*

In a study of 178 healthy pregnant women between the 7th and the 42nd week of pregnancy, it was found that erythropoietin (EPO) and vitamin B12 act together to establish normal erythropoiesis in pregnancy. *(N. Carretti, et al, Gynecol Obstet Invest 1995;39(2):83-7)*

The infant of a mother with subclinical asymptomatic vitamin B12 deficiency and decreased breast milk B12 can develop symptomatic B12 deficiency, including vomiting, failure to thrive, and megoblastic anemia. *(D.K. Grange, et al, Pediatr Hematol Oncol 1994 May-Jun;11(3):311-8)*

Chronic exposure to ambient nitrous oxide levels may increase the incidence of spontaneous abortion and female infertility. Vitamin B12 supplements can reverse some of these effects. *(D.S. Ostreicher, et al, NY State Dent J 1994 Mar;60(3):47-9)*

The demand for vitamin B12 is high in the first 27 weeks of pregnancy due to increasing maternal and embryo-fetal erythropoiesis and in order to sustain normal maternal hemoglobin levels in the last weeks of pregnancy. *(N. Carretti, et al, Gynecol Obstet Invest 1994;38(2):78-81)*

Vitamin B12 may favour the absorption and utilisation of folic acid after 27 weeks of pregnancy. *(N. Carretti, et al, Gynecol Obstet Invest 1994;38(2):78-81)*

In a study of 81 cases of neural tube defect pregnancies compared to 247 control pregnancies, a significant correlation was found between plasma B12 and red cell folate in cases, but not in controls. The levels of folate and B12 where increased risk occurred were not those usually associated with deficiency. *(P.N. Kirke, et al, Q J Med 1993 Nov;86(11):703-8)*

Chronic exposure to methylcobalamin, a vitamin B12 analog, protects cortical neurons against glutamate cytotoxicity. *(A. Akaike, et al, Eur J Pharmacol 1993 Sep 7;241(1):1-6)*

Over 70% of patients were given nitrous oxide either for analgesia during labour or for delivery by Caesarean section. Patients with small serum concentrations of B12 were more rapidly inactivated by nitrous oxide, and were thus at a disadvantage during anaesthesia. *(M.J. Landon, et al, Br J Anaesth 1992 Jul;69(1):81-6)*

Treatment with vitamin B6 + vitamin B12 significantly reduced the rate of induced exencephaly *23%) spina bifida occulta (80%), palate and rib malformations, kidney abnormalities and fetal weight retardation in mice. *(M.M. Elmazar, et al, Fundam Appl Toxical 1992 Apr;18(3):389-94)*

At least part of the genetic predisposition to neural tube defects, and possible other midline defects, could reside in an abnormality connected with vitamin B12 production, transport or metabolism. *(P. Gerdiki-Kouidou, et al, Clin Genet 1988 Jun;33(6):441-8)*

Given our findings, assessment of vitamin D status might be considered as a part of routine infertility workup since appropriate supplementation of those deemed depleted vitamin D might translate to improved fertility outcome and improved overall health *(Sebiha Ozkan, M.D., Sangita Jindal, Ph.D., Keri Greenseid, M.D., Jun Shu, M.D., Gohar Zeitlian, M.D., Cheryl Hickmon, B.S., Lubna Pal, M.B., B.S. Volume 94, Issue 4, Pages 1314-1319)*

A study aimed to evaluate whether the availability of vitamin B-12 and folate and the expression or activity of the target enzymes of the remethylation pathway are involved in NTD risk. The study concluded that decreased vitamin B-12 in liver and cord blood and decreased expression and activity of MS in liver point out the impaired remethylation pathway as hallmarks associated with NTD risk. The study suggested evaluating vitamin B-12 in the nutritional recommendations for prevention of NTD risk beside folate fortification or supplementation. *(Ma'atem B Fofou-Caillierez, Rosa-Maria Guéant-Rodriguez, Jean-Marc Alberto, Céline Chéry, Thomas Josse, Philippe Gérard, Thierry Forges, Bernard Foliguet, François Feillet, Jean-Louis Guéant, Vitamin B-12 and liver activity and expression of methionine synthase are decreased in fetuses with neural tube defects, The American Journal of Clinical Nutrition, Volume 109, Issue 3, March 2019, Pages 674–683)*

Low levels of vitamin B12 can increase the risk of NTDs. (*Molloy AM, et al. Pediatrics. 2009;123:917-923)*

Vitamin B6

Researchers found that poor preconception vitamin B6 status was associated with increased risk of early pregnancy loss and reduced probabilities of conception and clinical pregnancy in a prospective cohort of young Chinese women. The B vitamin status (folate, B6 and B12) of 364 women were examined and findings showed that sufficient levels of B6 improved the odds of conception by 40 per cent and lowered the odds for early pregnancy loss by 30 per cent, compared to women with B6 deficiency. This study underscores the potential importance of micronutrient status at the time of conception on pregnancy outcome. *(A.G. Ronnenberg et al . Preconception B-Vitamin and Homocysteine Status, Conception, and Early Pregnancy Loss.* Am J Epidemiol. 2007 Aug 1;166(3):304-12.)

Periconceptional intake of thiamine, niacin and pyridoxine seems to contribute to the prevention of OFC.(Krapels IP, van Rooij IA, Ocke MC, van Cleef BA, Kuijpers-Jagtman AM, Steegers-Theunissen RP. 2004. Maternal dietary B vitamin intake, other than folate, and the association with orofacial cleft in the offspring. *Eur J Nutr*. 43(1), 7-14)

Schulze-Bonhage A, Kurthen M, Walger P, Elger CE. 2004. Pharmacorefractory status epilepticus due to low vitamin B6 levels during pregnancy. *Epilepsia*, 45(1), 81-4.

Czeizel E, Kalina A. 2003. Public health control of hyperhomocysteinemia and its consequences. Orv Hetil, 144(40):1981-9

Minimal maternal dietary vitamin B6 supply of 3.1 mg per kg diet is necessary with regard to health and development of their offspring (Roth-Maier DA, Kettler SI, Benedikt J, Kirchgessner M. 2000. Effects of vitamin B6 supplementation in rats during lactation on vitamin B6 concentration and transaminase activities in the offspring. *Arch Tierernahr,* 53(3), 227-39)

McCarty MF. 2000. Prenatal high-dose pyridoxine may prevent hypertension and syndrome X in-utero by protecting the fetus from excess glucocorticoid activity. *Med Hypotheses,* 54(5), 808-13

In healthy pregnant women, according to a study, a daily supplement of 2 mg Pyridoxine Hydrochloride provides the adequacy of maternal and neonatal vitamin B6 status and the satisfactory growth of neonates at birth (Chang SJ. 1999. Adequacy of maternal pyridoxine supplementation during pregnancy in relation to the vitamin B6 status and growth of neonates at birth. *J Nutr Sci Vitaminol,* 45(4), 449-58)

In a German study of 458 women, between 40 and 60 percent were found to be low in vitamin B6 on all the criteria measured. A daily intake of at least 10mg of vitamin B6 has been calculated to be needed by a pregnant woman if the metabolism is to be maintained at the same level as that of a non-pregnant female of the same age.

During pregnancy, the additional oestrogen in the body can have a negative effect on the uptake of vitamin B6. If this is added to an existing shortage, created by prolonged use of the contraceptive pill, the deficiency can be more pronounced.

Vitamin B6 is needed for the production of red blood cells and antibodies. A co-enzyme in protein, fat and carbohydrate metabolism. The deficiency of B6 during pregnancy is one of the factors indicated in toxaemia of pregnancy (Preeclampsia). *(Wisconsin Univ., Vitamins & Hormones, Vol 36, 53-99, 1978)*

Induced cleft palate can be prevented both in number and severity by administration of vitamin B6 in rats. *(C. Jacobsson, et al, Cleft Palate Craniofac J 1997 Mar;34(2):95-100)*

In a study of lactating mothers given 1 mg/day pyridoxine hydrochloride throughout lactation, 54% of whom had used vitamin B6 supplement during pregnancy, findings suggested that gestationally accumulated stores are important for the maintenance

of adequate vitamin B6 status of infants during the early months. *(K. Heiskanen, et al, J Pediatr Gastroenterol Nutr 1996 Jul;23(1):38-44)*

An adequate vitamin B6 supply during lactation cannot compensate for a lack of vitamin B6 during gestation and vice versa a high dose of vitamin B6 during gestation did not completely protect against a suboptimal vitamin B6 during lactation. *(D.A. Roth-Maier, et al, Arch Tierernahr 1996;49(4):319-24)*

In a study on rats, an elevation in vitamin B6 supply during pregnancy led to an increase in blood vitamin B6 concentration of 40% and milk concentration of 79%. Treatment during lactation caused an increase of blood vitamin B6 concentration of 50% and in milk of 38%. *(J. Benedikt, et al, Int J Vitam Nutr Res 1996;66(2):146-50)*

In a study of 44 healthy infants, low vitamin B6 status observed between 4 and 6 months of age caused slower length growth, and from 6 to 9 months showed less length-for-age than similarly fed infants with higher vitamin B6 status. *(K. Heiskenen, et al, Pediatr Res 1995 Nov;38(5):740-6)*

Numerous studies have suggested that pregnant and lactating women may have dietary intakes of vitamin B6 that are well below the recommended dietary allowance, which may affect the vitamin B6 status of their offspring. *(T.R. Guilarte, Nutr Rev 1993 Jul;51(7):193-8)*

Vitamin B6 is an essential cofactor in the developing central nervous system and may influence brain development and cognitive function. Recent work in animal models suggests that vitamin B6 deficiency during gestation and lactation alters the function of a subtype of receptors thought to play an important role in learning and memory. *(T.R. Guilarte, Nutr Rev 1993 Jul;51(7):193-8)*

Administration of vitamin B6 and B12 significantly reduced induced spina bifida occulta (80%), palate and rib malformations, kidney abnormalities, and fetal weight retardation in mice. *(M.M. Elmazar, et al, Fundam Appl Toxicol 1992 Apr;18(3):389-94)*

In a double-blind, placebo-controlled study of 59 pregnant women, of 31 women given 25 mg vitamin B6 every 8 hours for 72 hours, 15 had vomiting before therapy, compared to 8 after therapy. In the control group given placebo, 10 of 28 women had vomiting before therapy, compared to 15 afterwards. *(V. Sahakian, et al, Obstet Gynecol 1991 Jul;78(1):33-6)*

Maternal and cord vitamin B6-metabolizing enzymes are significantly correlated. *(R. Delport, et al, Nutrition 1991 Jul-Aug;7(4):260-4;discussion 264-6)*

In a study of 20 lactating women given supplemental doses of vitamin B6 0.5 to 4 mg daily beginning 24 hours after delivery for the first 9 months postpartum, plasma pyridoxal phosphate and breast milk total vitamin B6 concentrations were elevated

without reducing plasma prolactin concentrations or halting lactation. *(M.B. Andon, et al, Pediatrics 1985 Nov;76(5):769-73)*

In a study of 30 pregnant rats, tissue saturation was reached at a supply of 6 ppm of vitamin B6, and retention plateaued. At higher supplementation levels no further effect was found on concentrations in fetuses, placenta, amniotic fluid, amnion, uterus, or mammary glands. *(M. Kirchgessner, et al, Ann Nutr Metab 1985;29(3):138-46)*

In a study of 127 pregnant women, infants of mothers who were vitamin B6 deficient had lower Apgar scores than those of mothers with adequate vitamin B6 status. *(K. Schuster, et al, Am J Clin Nutr 1981 Sep;34(9):1731-5)*

Vitamin B1 (Thiamine)

Thiamine is essential for glucose oxidation, insulin production by pancreatic beta-cells and cell growth. It is therefore likely that thiamine supplementation in pregnant women not only improves their glucose tolerance but also stimulates the intra-uterine growth, thereby preventing a low birth weight to ensue from conventional therapy which only improves glucose tolerance (Bakker SJ, ter Maaten JC, Gans RO. 2000. Thiamine supplementation to prevent induction of low birth weight by conventional therapy for gestational diabetes mellitus

Thiamine deficiency remains an important public health problem in some populations (Ortega RM, Martinez RM, Andres P, Marin-Arias L, Lopez-Sobaler AM. 2004. Thiamine status during the third trimester of pregnancy and its influence on thiamine concentrations in transition and mature breast milk. *Br J Nutr,* 92(1), 129-35)

Vitamin B1 is needed for a wide range of functions including carbohydrate metabolism and energy production. In late and post-delivery, thiamine requirements are greatly increased.

In a study of 13 preterm infants, 45 full-term infants and their mothers, plasma thiamine concentrations in umbilical veins in both groups were seven times greater in infants than in mothers. *(G. Link, et al, Int J Vitam Nutr Res 1998;68(4):242-8)*

In a study on rats, a suboptimal supply of thiamine was not compensated for an intensified transfer of reserved body thiamine into milk. *(D.A. Roth-Maier, et al, Z Ernahrungswiss 1997 Jun;36(2):169-75)*

Data from rats indicates that an adequate thiamin supply during lactation cannot completely compensate for an inadequate thiamin supply during gestation. A constant thiamin supply is necessary. *(M. Kirchgessner, et al, Int J Vitam Nutr Res 1997;67(4):248-54)*

Mean serum levels of thiamin do not differ significantly between trimesters, but there is a significant decrease in the mean red blood cell thiamin levels in the third trimester. *(G.C. Icke, et al, Int J Vitam Nutr Res 1994;64(1):33-5)*

In a study of 20 nonpregnant women and 60 pregnant women, the occurrence of deficient thiamin status demonstrated an increase with the number of previous pregnancies. *(S.C. Vir, et al, Int J Vitam Nutr Res 1980;50(2):131-40)*

A study on rats indicated that the developing brain is vulnerable to reduced thiamin intake and that the period of vulnerability may be different for activity and avoidance learning. *(J.M. Bell, et al, J Nutr 1979 Sep;109(9):1577-83)*

A study indicated that pregnant rats had a 19% higher liver content of vitamin B1 than non pregnant rats. The requirement of vitamin B1 for pregnant rats was calculated to be almost double that of non-pregnant rats. *(S. Rajtek, et al, Arch Tierernahr 1990 Oct;40(10):901-13)*

The result of a study on pregnant mothers indicates that maternal thiamin deficiency may be one cause of intrauterine growth retardation. *(T. Heinze, et al, Z Ernahrungswiss 1990 Mar;29(1):39-46)*

A study in rats suggested that the thiamin fixation in tissues in offspring occurs prior to the fixation in the lactating mother. *(F. Hammoudia, et al, Int J Vitam Nutr Res 1980;50(4):370-9)*

In a study of 131 healthy mothers with normal pregnancies and deliveries across 12 countries, 85.2% of infants born to mothers deficient in thiamin also had inadequate status. Maternal deficiencies in more than one of vitamins B1, B2, or B6 further increased the risk of infant thiamin deficiency. *D.J. Sanchez, et al, Eur J Clin Nutr 1999 Jan;53(1):27-38)*

Vitamin B2 (Riboflavin)

Kim KN, Kim YJ, Chang N. 2004. Effects of the interaction between the C677T 5,10-methylenetetrahydrofolate reductase polymorphism and serum B vitamins on homocysteine levels in pregnant women. *Eur J Clin Nutr,* **58**(1), 10-6.

Riboflavin deficiency should be considered a possible risk factor for preeclampsia. Insufficient concentrations of the riboflavin-derived cofactors flavin adenine dinucleotide and flavin adenine mononucleotide could contribute to the established pathophysiologic changes including mitochondrial dysfunction, enhanced oxidative stress, and disturbances in nitric oxide release (Wacker J, Fruhauf J, Schulz M, Chiwora FM, Volz J, Becker K. 2000. Riboflavin deficiency and preeclampsia. *Obstet Gynecol,* **96**(1), 38-44)

Women with preeclampsia have been shown to have higher homocysteine levels (Maruotti G, Del Bianco A, Amato AN, Lombardi L, Fulgeri AM, Pietropaolo F. 2005. Preeclampsia and high serum levels of homocysteine. *Minerva Ginecol*, **57**(2), 165-70

Vitamin B2 supplementation may also help regulate the levels of Homocysteine.

Involved in protein and energy metabolism.

Supplementation of riboflavin may result in increased absorption of zinc and iron, and may therefore have a direct as well as an indirect effect on growth. *(V.V. Agte, et al, Biol Trace Elem Res 1998 Nov;65(2):109-15)*

Significant improvement was shown in mean weight gain in pregnancy, mean weight of pups and percentage haemoglobin with riboflavin supplementation in mice. *(V.V. Agte, et al, Biol Trace Elem Res 1998 Nov;65(2):109-*

Riboflavin deficiency in pregnancy could be only partially compensated by an optimal supply in lactation in rats. *(G. Hirschvogl, et al, Arch Tierernahr 1997;50(3):245-56)*

In a study of 372 pregnant women, maternal intake of riboflavin was positively associated with fetal growth. *(A. Badart-Smook, et al, J Am Diet Assoc 1997 Aug;97(8):867-70)*

The administration of antibodies which cause riboflavin deprival in mice resulted in progressive alteration in the fetal hepatic structure, eventually leading to fetal wastage and termination of pregnancy. *(U. Natraj, et al, Am J Reprod Immunol 1989 Jan;19(1):6-10)*

The levels in human cord serum of proteins capable of binding to riboflavin increase after 4 months and remain significantly elevated up to 8 months. Although the level of the protein in the maternal serum remains low until 4 months, its level in the amniotic fluid is elevated 2-3 fold as compared to that in serum. *(U. Natraj, et al, J Reprod Immunol 1988 Jun;13(1):1-16)*

An equilibrium in placental transfer of riboflavin is reached when the concentration is lowest on the maternal side, highest in the placenta, and intermediate on the fetal side. The transplacental gradient to the fetus was lower at high concentrations of riboflavin. *(J. Dancis, et al, Am J Obstet Gynecol 1988 Jan;158(1):204-10)*

In a study of 20 uneventful pregnancies, the cord serum concentration of riboflavin was generally higher than the maternal concentration. There was no detectable difference in the binding of riboflavin to proteins in cord and maternal serum. *(N.W. Kirshenbaum, et al, Am J Obstet Gynecol 1987 Sep;157(3):748-52)*

During gestation iron is diverted from maternal tissues to satisfy fetal requirements. Iron-mobilising activity in placental mitochondria was reduced in riboflavin deficient rats, but concentrations of iron in fetal tissues were unaffected. The primary effect of riboflavin deficiency appears to be a reduction in fetal mass, which serves to limit maternal iron depletion and maternofetal iron transfer. *(H.J. Powers, J Nutr 1987 May;117(5):852-6)*

In a study of 19 women given 0.3 mg riboflavin daily from 2 to 12 weeks after delivery compared to 20 similar women without supplements, the concentration of riboflavin in milk increased with supplementation of the mothers. *(K.A. Ronnholm, Am J Clin Nutr 1986 Jan;43(1):1-6)*

In a study of 44 pregnant women, the concentration of free riboflavin was higher in the umbilical artery than in the umbilical vein, indicating a release of free riboflavin from fetal tissues independent of gestational age. *(J. Zempleni, et al, Pediatr Res 1995 Oct;38(4):585-91)*

Measurements of riboflavin concentration in tissues in rats show that when riboflavin is given in suboptimal quantity, it is fixed by the foetus first. *(J. Leclerc, et al, Int J Vitam Nutr Res 1979;49(1):51-8)*

In a study of 131 healthy mothers with normal pregnancies and deliveries, maternal status of each individual vitamin (B1, B2 , and B6), but especially riboflavin, was affected by maternal status of the other vitamins. *(D.J. Sanchez, et al, Eur J Clin Nutr 1999 Jan;53(1):27-38)*

Vitamin B3 (Nicotinamide)

Vitamin B3 is essential for carbohydrate metabolism and the circulatory system. Increased vitamin B3 intake has been shown to be particularly important during pregnancy.

Higher concentrations of nicotinamide in the maternal serum have been associated with a lower risk of exzema in babies at 12 months age. *(Clin Exper Allergy doi: 10.1111/cea.12782)*

Study results indicate that female sex hormones inhibit the synthesis of niacin from trytophan. *(K. Shibata, et al, Biosci Biotechnol Biochem 1997 Jul;61(7):1200-2)*

In studies in cows, supplementary niacin increased microbial protein synthesis in vitro and in vivo, and prevented the postpartum decrease in red blood cell niacin observed in controls. *(B.E. Brent, et al, J Anim Sci 1984 Sep;59(3):813-22)*

Vitamin E

Agarwal A, Gupta S, Sharma RK. 2005. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol, **3**(1), 28

Poston L, Raijmakers M, Kelly F. 2004. Vitamin E in preeclampsia. *Ann N Y Acad Sci*, 1031, 242-8.

Beazley D, Ahokas R, Livingston J, Griggs M, Sibai BM. 2005. Vitamin C and E supplementation in women at high risk for preeclampsia: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol,* **192**(2), 520-1

Llurba E, Gratacos E, Martin-Gallan P, Cabero L, Dominguez C. 2004. A comprehensive study of oxidative stress and antioxidant status in preeclampsia and normal pregnancy. *Free Radic Biol Med,* **37**(4), 557-70

Needed by muscles and blood vessels, and also a major antioxidant. Up to 200IU of vitamin E has been shown to be helpful in the prevention of miscarriages.

In vitro vitamin E accelerated hypoplastic fetal lung growth in rats, and in vivo vitamin E significantly increased lung weights, total DNA, and protein contents. *(S. Islam, et al, J Pediatr Surg 1999 Jan;34(1):172-6 discussion 176-7)*

In a study on diabetic pregnant rats and their neonates, results suggested that they are exposed to an increased oxidative stress, but that vitamin E supplementation during pregnancy could at least in part reduce its detrimental effects. *(M. Kinalski, et al, Przegl Lek 1998;55(6):320-4)*

In a study of 20 preeclamptic, 25 normotensive pregnant and 25 healthy non-pregnant women, preeclamptic women showed a highly significant fall in vitamin E levels compared to controls, supporting the view that increased lipid peroxidation may be involved in vasoconstriction in preeclampsia. *(S. Kharb, et al, Gynecol Obstet Invest 1998;46(4):238-40)*

A study on 10 pregnant women given 1 g vitamin E daily for three days before delivery found that plasma and red blood cell vitamin E was dramatically increased in mothers, but not in neonates. This suggests that transfer of vitamin E through the placenta may be low, or that it may be restricted by the paucity of lipids circulating in the blood of neonates. *(C.L. Leger, et al, Int J Vitam Nutr Res 1998;68(5):293-9)*

Concentrations of antioxidants in breast milk probably define the degree of protection it can offer against peroxidation. Vitamin E concentrations in mature milk have been found to be significantly lower in smokers than non-smokers. This may aggravate peroxidation events already known to be favoured in the newborns of maternal smokers. *(R.M. Ortega, et al, Am J Clin Nutr 1998 Sep; 68(3):662-7)*

In a study of 36 healthy pregnant women and 92 women with hypertension, lipid peroxides in serum and placental tissue were significantly increased, and vitamin E levels in serum were significantly decreased in women with severe gestational hypertension and preeclampsia compared with controls. *(E. Gratacos, et al, Am J Obstet Gynecol 1998 May; 178(5):1072-6)*

In a study of 1,302 ewes, vitamin E supplementation during pregnancy significantly reduced lamb mortality compared with no supplementation in the early part of the lambing season. *(R.W. Kott, et al, J Am Vet Med Assoc 1998 Apr 1;212(7):997-1000)*

Supplementation with vitamin E succinate and ellagic acid significantly decreased fetal growth retardation, fetal death and placental weight reduction induced by oxidative damage in mice. Treatment also resulted in a 77-88% reduction in the production of superoxide anion, a 70-87% decrease in the production of lipid peroxidation, and a 21-47% decrease in DNA single strand breaks in embryonic and placental tissues. *(E.A. Hassoun, et al, Toxicology 1997 Dec 19;124(1):27-37)*

Supplementation with 2% wt/wt of vitamin E in diabetic rats (diabetes is associated with disturbed embryogenesis due to excess oxygen radical activity) clearly prevented congenital malformations. Increased concentrations of vitamin E were found in maternal, embryonic, and fetal tissues. *(C.M. Siman, et al, Diabetes 1997 Jun;46(6):1054-61)*

In a study of 25 pregnant women given 300 mg daily vitamin E from week 6-12 of gestation throughout pregnancy for treatment of uterine myomas, the neonatal outcome was satisfactory in all cases and no collateral effects were observed in either mothers or fetuses. *(L. Fruscella, et al, Minerva Ginecol 1997 Apr;49(4):175-9)*

Chicks hatched from hens supplemented with vitamin E had significantly higher antibody titers at days 1 and 7 of age than chicks from controls. Vitamin E supplementation of breeder birds increased the immune response of their progeny. *(A.U. Haq, et al, Poult Sci 1996 Sep;75(9):1092-7)*

Administration of vitamin E to diabetic animals decreases the rate of embryo malformations and increases their size and maturation. *(M. Viana, et al, Diabetologia 1996 Sep;39(9):1041-6)*

The serum vitamin E levels of preeclamptic and eclamptic women were 15% and 30% lower, respectively, than those of corresponding controls, supporting the hypothesis that preeclampsia and eclampsia deplete natural lipid antioxidants. *(S.A. Ziari, et al, Am J Perinatol 1996 Jul;13(5):287-91)*

Studies suggest that the lactation stage affects serum vitamin E concentrations by influencing both the concentration of lipoprotein particles and the concentration of vitamin E within individual particles. *(T.H. Herdt, et al, J Vet Diagn Invest 1996 Apr;8(2):228-32)*

In a study of 26 mothers and their full-term placental cords at delivery, elevated blood levels of vitamin E-quinone in newborns compared to their mothers suggest increased oxidative stress and utilisation of vitamin E in newborns. Because vitamin E levels in red blood cells of newborns are lower and significantly related to vitamin E levels in red blood cells of their mothers, an increase in vitamin E supplementation to mothers during pregnancy may increase vitamin E levels in the newborn and help impede the effect of extrauterine oxygen toxicity. *(S.K. Jain, et al, J Am Coll Nutr 1996 Feb;15(1):44-8)*

In vitro lipid peroxidation was found to be highest in rat pups nursing from dams with low vitamin E status, the magnitude of which was greatest in heart and liver microsomes. *(H.E. Pazak, et al, Int J Vitam Nutr Res 1996;66(2):134-40)*

In a study on rats, placental transfer of vitamin E was preferentially incorporated into heart and lung tissue during gestation, with a low transfer to fetal liver. All tissues, but especially the liver, had an increased vitamin E content following birth when nursed by dams supplemented with vitamin E. *(H.E. Pazak, et al, Int J Vitam Nutr Res 1996;66(2):126-33)*

High doses of antenatal vitamin E were found to protect newborn rat pups against hypoxia-induced tissue injury. *(C. Inan, et al, Pediatr Res 1995 Nov;38(5):685-9)*

In a study of 49 normotensive and 11 hypertensive pregnant women, hypertensive women had significantly lower vitamin E and higher MDA (an end product of lipid peroxidation) levels. Higher diastolic blood pressure correlated with the extent of vitamin E deficiency and increased MDA levels. *(S.K. Jain, et al, Mol Cell Biochem 1995 Oct 4;151(1):33-8)*

From a study of 24 pregnant women it was concluded that more then 85% of the mothers in the current population would benefit from vitamin E supplementation from the viewpoint of the fetal red blood cell vitamin E requirement in spite of the rather high maternal lipid normalised vitamin E plasma content. *(O. Cachia, et al, Am J Obstet Gynecol 1995 Jul;173(1):42-51)*

In a study on cows fed 0 or 200 g supplemental fat and 0 or 890 IU supplemental vitamin E daily starting 14 days prior to anticipated calving, supplemental dietary fat elevated plasma concentrations of both vitamin E and beta-carotene in relation to increased plasma cholesterol levels. For colostrum, dietary vitamin E increased concentrations of alpha-tocopherol and decreased concentrations of beta-carotene. *(W.P. Weiss, et al, J Dairy Sci 1994 May; 77(5):1422-9)*

In studying the plasma levels of vitamin E and total lipids in the plasma of 80 pregnant women and their placental cords at normal delivery, the concentration of vitamin E correlated with that of total lipids in both plasma. The ratio of vitamin E to total lipids in the mother also correlated with the ratio in the cord, suggesting that lipids in serum are a regulatory factor. It seems that the fetus has a unique lowered vitamin E level due to the effects of the accelerated lipid metabolism in the fetus. *(Y. Mizumoto, et al, Nippon Sanka Kujinka Gakkai Zasshi 1994 Apr; 46(4):315-21)*

In a study of 80 pregnant women at delivery, the vitamin E / total lipid ratio in the plasma of the mother and of the placental cord was inversely correlated with the concentration of lipid peroxides. *(Y. Mizumoto, et al, Nippon Sanka Kujinka Gakkai Zasshi 1994 Apr; 46(4):315-21)*

In pregnancies with fetal complications or maternal risks, mean maternal vitamin E levels in serum were lower than in normal pregnancies at corresponding gestational age. *(U. von Mandach, et al, Int J Vitam Nutr Res 1994;64(1):26-32)*

In EPH gestosis, the plasma levels of lipid peroxides increased while the levels of vitamin E which inhibited their formation decreased in plasma, red cells and platelets. *(H. Iioka, Gynecol Obstet Invest 1994;38(3):173-6)*

A study on pregnant sows found that vitamin E restriction depressed peripheral blood lymphocyte (PBL) and polymorphonucear cell (PMN) immune functions. *(H. Wuryastuti, et al, J Anim Sci 1993 Sep; 71(9):2464-72)*

In the case of a woman who had chronically consumed megadose amounts of vitamins A, B1, B6, B12 and vitamins C and E, long term intake of 99 times the RDA of vitamin E resulted in milk vitamin E levels that were more than three times above the upper range of normal. *(D.M. Anderson, et al, J Am Diet Assoc 1985 Jun;85(6):715-7)*

It is hypothesised that the interaction of maternal components, particularly neutrophils and oxidation-susceptible lipids, with placental cells and placental-derived factors engenders feed-forward cycles of oxidative stress that ultimately cause widespread endothelial cell dysfunction and its clinical manifestations, including preeclampsia. *(C.A. Hubel, Semin Reprod Endocrinol 1998;16(1):75-92)*

Betacarotene

The authors examined concentrations of beta-carotene, retinol and alpha tocopherol were measured in ovarian follicular fluid and plasma samples collceted at the time of oocyte recovery from patients enrolled in an in vitro fertilization program. It was found that smokers had much lower levels of betacarotene, suggesting the possible role of the antioxidant betacarotene as a biological marker on ovarian oocyte follicular maturation and function. *(Palan PR et al. 1995 Gynecol Obstet Invest ; 39(1):43-6)*

Meram I, Bozkurt AI, Kilincer S, Ozcirpici B, Ozgur S. 2004. Vitamin A and beta-carotene levels during pregnancy in Gaziantep, Turkey. *Acta Medica (Hradec Kralove),* **47**(3), 189-93.

Zinc supplementation during pregnancy improved the vitamin A status of mothers and infants postpartum, which indicates a specific role of zinc in vitamin A metabolism. Addition of both beta-carotene and zinc to iron supplements during pregnancy could be effective in improving the vitamin A status of mothers and infants (Dijkhuizen MA, Wieringa FT, West CE, Muhilal.2004. Zinc plus beta-carotene supplementation of pregnant women is superior to beta-carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr,* **80**(5),1299-307)

Converted to vitamin A by the body. Needed for bone development, skin maintenance, resistance to infection, and vital as a major antioxidant.

Deficiency of vitamin A has been implicated in foetal malformation. *(Pathol Biol 10:119, 1962)*

Neither teratogenicity nor vitamin A toxicity has been observed in multiple species exposed to high doses of beta-carotene. *(R.K. Miller, et al, Reprod Toxicol 1998 Jan-Feb;12(1):75-88)*

Beta-carotene may be a precursor of retinol in the placenta and this conversion may depend on the nutritional status of the mother, being particularly effective in a more depleted state. *(R. Dimenstein, et al, Biol Neonate 1996;69(4):230-4)*

Kidney exposure to retinoic acid during development led to a six-fold increase in nephron formation and a significantly more developed branching pattern of the ureteric bud in isolated rat organs, with a greater effect seen at a younger age. *(J. Vilar, et al, Kidney Int 1996 May;49(5):1478-87)*

In a study of 1725 women (of whom 58 were pregnant), the use of a vitamin A containing (maximum 1200 RE) multivitamin supplement contributed to a controlled and adequate vitamin A intake, and was considered as safe for pregnant women or women who wish to become pregnant, if the consumption of liver was completely avoided. *(H. van den Berg, et al, Eur J Obstet Gynecol Reprod Biol 1996 May;66(1):17-21)*

Vitamin A is required during pregnancy for fetal lung development. Vitamin A deficiency in rats caused lesser development of bronchial passageways, reduced elastic fibers, and reduced relative air space and size of sacculi. *(C. Antipatis, et al, Am J Physiol 1998 Dec;275(6 Pt 1):L1184-91)*

From a study of 35,727 pregnant women, use of low or moderate doses of vitamin A (<10,000 IU) during the first trimester of pregnancy was not teratogenic, but presented some protective effect to the fetus. *(A.E. Czeizel, et al, Int J Vitam Nutr Res 1998;68(4):219-31)*

Vitamin A (retinol) and retinoic acid have been shown to enhance the synthesis of phospholipid surfactant components. A partial vitamian A deficiency in rats led to a 21% decrease in lung surfactant phospholipids. During late pregnancy, the fetal lung stores surfactant in preparation of extrauterine life. Surfactant deficiency precipitates respiratory distress syndrome (RDS). *(B. Chailley-Heu, et al, Am J Respir Cell Mol Biol 1999 Jul 1;21(1):89-96)*

In a study of 40 women with habitual abortion compared to controls, levels of lipid peroxidation were increased and plasma levels of vitamin A, E and beta-carotene were decreased. *(M. Simsek, et al, Cell Biochem Funct 1998 Dec;16(4):227-31)*

Results of a trial in non-pregnant women document that daily oral supplements of 4000, 10,000, and 30,000 IU vitamin A given for 3 weeks resulted in plasma levels in the range or slightly above the range of plasma levels seen in early pregnancy. *(U.W. Wiegand, et al, IntJ Vitam Nutr Res 1998;68(6):411-6)*

In a study of the effect of mild vitamin A deficiency in rats, vitamin A supply to the fetus was critical in determining the number of organ nephrons in cases and controls. *(M. Lelievre-Pegorier, et al, Kidney Int 1998 Nov;54(5):1455-62)*

Blood levels of retinoids from women taking 30,000 IU/day preformed vitamin A are not greater than retinoid blood levels in pregnant women during the first trimester who delivered healthy babies. *(R.K. Miller, et al, Reprod Toxicol 1998 Jan-Feb;12(1):75-88)*

In a study of 57 healthy, lactating mothers, diet and nutritional status of vitamin A in the third trimester of pregnancy conditioned concentrations of this vitamin in maternal milk, with the effect particularly noticeable in mothers with intakes below recommended values. *(R.M. Martinez, et al, Med Clin (Barc) 1997 Nov 1;109(15):583-4)*

Regular vitamin A supplements may be safely used by pregnant women who consume little or no liver or liver products. *(H. van den Berg, et al, Ned Tijdschr Geneeskd 1996 Jan 27;140(4):192-5)*

In a study in Hackney, London, most of the mothers were marginal with respect to vitamins A, E and zinc. In those with low birthweight babies, a higher intake would have improved their nutritional status and possibly the outcome of their pregnancy. *(K. Ghebremeskel, Early Human Dev 1994 Nov 18;39(3):177-88)*

Vitamin C

The authors examined ascorbic acid in the follicular fluid of women treated with IVF and embryonic transfer and analysed the influence of vitamin c supplementation on the results of infertility treatment. The results showed that ascorbic acid levels in follicles were significantly higher in women with vitamin C supplementation than in the control group. Vitamin supplementation had a greater impact on the number of pregnancies in the non-smokers group. (Crha I et al. 2003 Cent Eur J Public Health:11 (2): 63-7)

Ascorbic Acid may prevent gametes from damage by free radicals during production and fertilization. The supply of ascorbic

acid to the ovary might be a limiting factor in the ability of the preovulatory follicle to grow in response to gonadotropin stimulation, therefore it may be involved with female fertility.(Luck MR. et al Biol Reprod 1995; 52(2):262-6)

Agarwal A, Gupta S, Sharma RK. 2005. Role of oxidative stress in female reproduction. *Reprod Biol Endocrinol*, 3(1), 28

Human milk Ascorbic acid (AA) can be doubled or tripled by increased intake of AA in women with low human milk AA content at baseline. The response to a relatively high dose of AA was modest in European women in contrast with the 3-fold increase in mean human milk AA content in African women. These data indicate that human milk AA content is regulated (Daneel-Otterbech S, Davidsson L, Hurrell R. 2005. Ascorbic acid supplementation and regular consumption of fresh orange juice increase the ascorbic acid content of human milk: studies in European and African lactating women. *Am J Clin Nutr,* 81(5), 1088-93)

Casanueva E, Ripoll C, Tolentino M, Morales RM, Pfeffer F, Vilchis P, Vadillo-Ortega F. 2005. Vitamin C supplementation to prevent premature rupture of the chorioamniotic membranes: a randomized trial. *Am J Clin Nutr,* 81(4), 859-63

Fischer T, Pildner von Steinburg S, Diedrich F, Neumaier-Wagner P, Paepke S, Jacobs VR, Schneider KT. 2005. Prevention of preeclampsia. *Zentralbl Gynakol,* 127(2), 83-90

Simsek M, Naziroglu M, Erdinc A. 2005. Moderate exercise with a dietary vitamin C and e combination protects against streptozotocin-induced oxidative damage to the kidney and lens in pregnant rats. *Exp Clin Endocrinol Diabetes,* 113(1), 53-9.

Vitamin C is especially important for the formation of immune system cells, and its antioxidant role to help protect against free radical damage.

Fetal plasma and placental and amniotic fluid vitamin C concentrations were found to be significantly higher in guinea pigs fed a high vitamin C diet, compared to those fed a diet with moderate intake of vitamin C. The degree to which maternal vitamin C intake influenced circulating levels of fetal vitamin C decreased with gestational age. (*S. Das, et al, Br J Nutr 1998 Nov;80(5):485-91)*

In a study of 57 women, non-smokers showed significantly greater vitamin C levels in both transition and mature milk. *(R.M. Ortega, et al, J Am Coll Nutr 1998 Aug;17(4):379-84)*

In a study of placentas from 29 normal women and 6 preeclamptic women, perfusion with 500 microM vitamin C or 50 microM vitamin E had no effect on lipid peroxidation or antioxidative enzymes in normal placentas, but reduced placental lipid peroxidation and potentiated the activity of some placental antioxidative enzymes in preeclamptic placentas. *(A.K. Poranen, et al, Acta Obstet Gynecol Scand 1998 Apr; 77(4):372-6)*

In a study of vitamin C uptake in the near-term human placenta, data suggested there was an intracellular pool of vitamin C which filled up with increasing plasma L-dehydroascorbic acid (a form of vitamin C) levels. *(C. Rybakowski, et al, Eur J Obstet Gynecol Reprod Biol 1995 Sep;62(1):107-14)*

There is a direct connection between vitamin C availability and increase in collagen degradation. This leads to a loss of mechanical support and eventual fetal membrane rupture. *(F. Vadillo Ortega, et al, Ginecol Obstet Mex 1995 Apr;63:158-62)*

In a study of 44 pregnant women, the leukocyte vitamin C levels throughout gestation showed a decrease towards week 28, and then recovered at the end of the pregnancy. The levels on week 20 showed an association with premature rupture of amniotic membranes. *(E. Casanueva, et al, Arch Med Res 1995;26 Spec No:S149-52)*

In a study on pregnant sows fed a vitamin C deficient diet, only a few showed clinical symptoms of vitamin C deficiency, but severe pathological changes were seen in the uterus and fetuses, including hemorrhages and hematomas in both fetal and maternal placenta, general edema and hemorrhages in the fetuses, severe derangment of ossification (of the skeleton), and the loosening of the periost from the cortex. *(I. Wegger, et al, J Nutr 1994 Feb;124(2):241-8)*

In a study of 10 women with premature rupture of chorioamniotic membranes (PRM) and 19 control women, low vitamin C levels were associated with PRM. Infections in the PRM group were more frequent when the women had low levels of vitamin C. *(E. Casanueva, et al, Eur J Clin Nutr 1991 Aug;45(8):401-5)*

In a study of plasma vitamin C concentrations in 200 mothers and their infants, the 19 with no risk factors, complications or diseases during pregnancy or delivery or in the infant showed great variability, as did concentrations across the entire group. *(P. Heinz-Erian, et al, Padiatr Padol 1987;22(2):163-78)*

In a study of 200 mothers, cord blood and newborn plasma vitamin C concentrations were nearly twice as high as maternal plasma concentrations, although they were correlated with maternal concentrations. Amniotic vitamin C concentrations were also correlated to maternal plasma concentrations, being about 3 times higher. *(P. Heinz-Erian, et al, Padiatr Padol 1987;22(2):163-78)*

In a study of 200 mothers, various diseases and risk factors in mother and/or child were shown to be associated with lower vitamin C concentrations. *(P. Heinz-Erian, et al, Padiatr Padol 1987;22(2):163-78)*

Deposition of collagenous matrix in amnion, which provides its mechanical strength and resistance to rupture, increases several fold when the vitamin C concentration in the supernatant medium is increased from 0 to 50 mcg/ml. *(J.D. Aplin, et al, Placenta 1986 Sep-Oct;7(5):377-89)*

In a comparison of preterm and term milk, vitamin C levels were higher in preterm milk during the first week of lactation. *(S.a. Udipi, et al, Am J Clin Nutr 1985 Sep;42(3):522-30)*

In a case study of a woman who had chronically consumed 40 times the RDA of vitamin C, milk vitamin C levels were elevated above established norms [but it is implied not by a large degree – Ed] *(D.M. Anderson, et al, J Am Diet Assoc 1985 Jun;85(6):715-7)*

In a study of 200 mothers, plasma concentrations of vitamin C in exclusively breast-fed infants was about 2-fold compared with maternal concentration. It was relatively independent of maternal nutrition and of vitamin C concentration in milk. The mother's intake of vitamin C influenced their plasma and milk concentrations. *(L Salmenpera, Am J Clin Nutr 1984 Nov;40(5):1050-6)*

Vitamin D

The authors investigated 67 infertile women and took vitamin D measures from them. Only 7 per cent of them had normal vitamin D levels and the rest had either insufficient levels or clinical deficiency.

The authors concluded that not a single patient with either ovulatory disturbance or polycystic ovary syndrome demonstrated normal Vitamin D levels; 39 per cent of those with ovulatory disturbance and 38 per cent of those with PCOS had serum 25OHD levels consistent with deficiency. The research may offer a simple, cheap and safe option for women to try before resorting to drugs. *(L . Pal , J et al 2008. Fertility and Sterility , Volume 90 , Pages S14 - S14)*

Sufficient preconception 25-hydroxyvitamin D (≥75 nmol/L) was associated with increased likelihood of pregnancy and livebirth. Increased vitamin D concentrations before conception, but not in early pregnancy, were associated with reduced pregnancy loss. *(Mumford et al. 2018, Lancet Diabetes & Endocrinology)*

To analyze the relationship between maternal serum 25-hydroxyvitamin D status and the prevalence of primary Caesarean delivery, the researchers measured maternal and infant vitamin D at birth from March 21, 2005 to March 20, 2007. Demographic and medical data were abstracted from the maternal medical records at an urban teaching hospital in Boston with 2,500 births a year.

The study included 253 women of whom 43 (17%) had a primary Caesarean. Reasons for Caesareans included failure to progress, non-reassuring fetal tracing, malpresentation such as breech, a cephalopelvic disproportion, and variable fetal heart rate. Of the women, 28% with serum vitamin D levels less than 37.5 nmol/L had a Caesarean delivery, compared with only 14% of women with vitamin D levels $\geq$37.5nmol/L (P=0.012). Discussing the findings, the researchers said that vitamin D deficiency has been associated with proximal muscle weakness, as well as with suboptimal muscle performance and strength. (Merewood A, et al "Association between vitamin d deficiency and primary caesarean section" J Clinical Endocrinol Metab 2008; DOI: 10.1210/jc.2008-1217.*)*

‘Vitamin D is essential for skeletal growth and bone health. Dietary sources in the UK are very limited and oily fish is the only significant source. The major natural source is from skin synthesis following exposure to sunlight. From mid-October to the beginning of April in the UK there is no ambient ultraviolet sunlight of the appropriate wavelength for skin synthesis of vitamin D.

For example, many health professionals and the public may be unaware that the skin cannot synthesise vitamin D from sunlight during winter months in the UK. They may also be unaware that a balanced diet alone will not provide sufficient vitamin D. In addition, they do not know enough about the importance of vitamin D supplements for at risk groups.

A newborn baby's vitamin D status is largely determined by the mother's level of vitamin D during pregnancy. Breastfed infants may need drops containing vitamin D from 1 month of age if their mother has not taken vitamin D supplements throughout pregnancy.

Breast milk is not a significant source of vitamin D.

The current reference nutrient intakes (µg/day) for vitamin D are:

- 8.5 for infants up to 6 months
- 7 for children between 6 months and 3 years
- 10 for women during pregnancy and lactation and adults over 65.

Currently there is no reference nutrient intake for people aged between 4 and 65 years. It is assumed that the action of sunlight on skin will provide adequate vitamin D, except for specific at-risk groups, such as women whose clothing conceals them fully or those confined indoors. ('Dietary reference values for food energy and nutrients for the United Kingdom. Report of the panel on dietary reference values of the Committee on Medical Aspects of food policy' Department of Health.)

At risk groups are currently advised to take a supplement that meets 100% of the reference nutrient intake for their age group (as above). The reference nutrient intake for at risk groups is 10 micrograms/day (1 microgram=40 international units, so 10 micrograms=400 IU).’

‘Vitamin D: Increasing supplement use among at-risk groups’, National Institute for Health and Care Excellence, Guidance PH56

“Gestational vitamin D deficiency was associated with higher scores on the Social Responsiveness Scale.”

“Another potential risk factor for Autism-spectrum Disorder is gestational vitamin D deficiency.”

‘Gestational vitamin D deficiency and autism-related traits: the Generation R Study’. AAE Vinkhuyzen, DW Eyles, THJ Burne, LME blanken, CJ Kruithof, F Verhulst, VW Jaddoe, H Tiemeier, JJ McGrath, Molecular Psychiatry, (2016) 00, 1-7

‘We present evidence that vitamin D is involved in female reproduction including IVF outcome (clinical pregnancy rates) and polycystic ovary syndrome (PCOS).

In PCOS women, low 25-hydroxyvitamin D (25(OH)D) levels are associated with obesity, metabolic, and endocrine disturbances and vitamin D supplementation might improve menstrual frequency and metabolic disturbances in those women.

Moreover, vitamin D might influence steroidogenesis of sex hormones (estradiol and progesterone) in healthy women and high 25(OH)D levels might be associated with endometriosis.

In men, vitamin D is positively associated with semen quality and androgen status. Moreover, vitamin D treatment might increase testosterone levels.'

'Vitamin D and fertility: A Systematic Review', Lerchbaum E, Obermayer-Pietsch B, European Journal of Endocrinology 2012; 166

Adequate vitamin D status/intake may help in the prevention and management of preeclampsia.

Hypponen E. 2005. Vitamin D for the prevention of preeclampsia? A hypothesis. *Nutr Rev,* 63(7), 225-32

Maternal vitamin D status in the second trimester was inversely associated with risk of early-onset pre-eclampsia and preterm birth at <35 weeks in women at high risk for pre-eclampsia. Compared to women with 25(OH)D levels of at least 75nmol/l, vitamin D deficient women were 2.40-fold more likely to develop early onset pre-eclampsia. AD Gernand, HN Simhan, KM Baca, S Caritis, LM Bodnar Vitamin D, pre-eclampsia, and preterm birth among pregnancies at high risk for pre-eclampsia: an analysis of data from a low-dose aspirin trial*, BJOG,* 10.1111/1471-0528.14372

Schroth RJ, Lavelle CL, Moffatt ME. 2005. Review of vitamin D deficiency during pregnancy: who is affected? *Int J Circumpolar Health,* 64(2),112-20

Reichrath J, Querings K. 2005. Vitamin D deficiency during pregnancy: a risk factor not only for fetal growth and bone metabolism but also for correct development of the fetal immune system? *Am J Clin Nutr,* 81(5), 1177

Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. 2005. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr,* 81(5), 1060-4.

Shenoy SD, Swift P, Cody D, Iqbal J. 2005. Maternal vitamin D deficiency, refractory neonatal hypocalcaemia, and nutritional rickets. *Arch Dis Child,* 90(4), 437-8.

Hirota K. 2003. Calcium and vitamin D metabolism during pregnancy and lactation. *Clin Calcium,* 13(7), 892-6

Prevention of Multiple Sclerosis by modifying an important environmental factor (sunlight exposure and vitamin D level) offers

a practical and cost-effective way to reduce the burden of the disease in the future generations (Chaudhuri A. 2005. Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis, *Med Hypotheses,* 64(3), 608-18)

Hollis BW, Wagner CL. 2004. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 79(5), 717-26

Needed for efficient utilisation and absorption of phosphorous, and calcium for developing bones.
Vitamin D is needed for efficient utilisation and absorption of phosphorous, and calcium for developing bones.

In a cross-racial study of 121 women, plasma levels of vitamin D in newborn infants averaged 67% of their mothers' vitamin D levels. Vitamin D concentrations of 60 – 70% maternal levels may represent a "normal" range for newborn infants. *(B. Waiters, et al, J Am Coll Nutr 1999 Apr;18(2):122-6)*

Levels of calcium absorption factors are increased in late gestation and early lactation in rats, perhaps mediated by vitamin D3 concentrations, in order to meet increased calcium demands of pregnancy and lactation. *(Y. Zhu, et al, Endocrinology 1998 Aug;139(8):3520-4)*

The major sources of vitamin D are sunlight exposure and supplemented formulas; in fact, the amount of vitamin D in breast milk, cow's milk, and common foods is poor. Although sunlight exposure should be able to maintain adequate vitamin D stores, a supplement with 400 IU/day of vitamin D from birth to the second year of life is recommend to assure the prophylaxis of rickets in all breast-fed infants. A dose of 400 IU/day of vitamin D is safe and appropriate. *(G. Saggese, et al, Ann Ist Super Sanita 1995;31(4):461-79)*

In a 3 month longitudinal study of 52 neonates from 3-6 days after delivery onwards, fed formula and given oral supplements of 500 or 1000 IU vitamin D, no toxic effect was observed whatever the vitamin D intake in neonates with no sign of vitamin D deficiency at the beginning of the study. *(F. Zeghoud, et al, Am J Clin Nutr 1997 Mar;65(3):771-8)*

In a study of 80 neonates and their mothers, 24% of neonates born to unsupplemented mothers were vitamin D deficient. *(F. Zeghoud, et al, Am J Clin Nutr 1997 Mar;65(3):771-8)*

In a study of 64 infants aged 1 to 4 months given oral vitamin D (500 to 1000 IU per day) and fed vitamin D fortified formula, no significant vitamin D overload was observed. *(C. Vervel, et al, Arch Pediatr 1997 Feb;4(2):126-32)*

In a study of 30 women, a positive correlation was found between the level of ionised calcium in maternal serum and the crown-heel length of the infant. This indicated that vitamin D deficiency affects fetal growth through an effect on maternal

calcium homeostasis. *(L. Brunvand, et al, Early Human Dev 1996 Jul 5;45(1-2):27-33)*

In a study of 65 infants presented with hypocalcaemic seizures and subsequently found to have rickets, maternal vitamin D deficiency and non-supplementation in the infants were the likely causes. Prophylactic vitamin D 400 IU administered to infants up to 2 years and 800 IU to women in pregnancy and during lactation is recommended to prevent vitamin D deficiency. *(I. Ahmed, et al, Acta Paediatr 1995 Aug;84(8):941-2)*

In a study of rats fed either a low vitamin D or a vitamin D supplemented diet prior to becoming pregnant and throughout pregnancy and suckling, maternal consumption of a low vitamin D diet resulted in a general but significant slowing of neonatal cardiac development. *(G.S. Morris, et al, J Mol Cell Cardiol 1995 Jun;27(6):1245-50)*

In countries without vitamin D supplementation of milk, a prevention of vitamin D deficiency through vitamin D supplementation is a necessity in pregnant women. This can be done with a daily supplement of 400 IU during all pregnancy, or a daily supplement of 1,000 IU during the third trimester. *(Arch Pediatr 1995 Apr;2(4):373-6)*

Studies in European and other countries have shown that vitamin D deficiency during pregnancy may adversely affect fetal growth, bone ossification, tooth enamel formation and neonatal calcium homeostasis.

Mothers at risk of vitamin D deficiency are those who avoid diary products and those who live in more northern latitudes. *(B.L. Specker, AmJ Clin Nutr 1994 Feb;59(2 Suppl):484S-490S; discussion 490S-491S)*

Poor maternal vitamin D status during lactation results in low breast milk vitamin D. *(B.L. Specker, AmJ Clin Nutr 1994 Feb;59(2 Suppl):484S-490S; discussion 490S-491S)*

In a longitudinal study of 27 low birth-weight and 25 full-term infants from birth to 16 weeks after delivery receiving vitamin D supplements, data document that 400 IU vitamin D represents a sufficient daily intake for both groups. *(W.B. Pittard, et al, Am J Dis Child 1991 Oct:145(10):1147-9)*

The effect on rat pups of supplementing lactating dams with large amounts of vitamin D was an improvement in neonatal growth. This was due to a significant increase in protein, RNA and DNA contents (without a change in the protein/DNA ratio), and an increased ash and dry bone weight (again, with no change in the ash/dry bone weight ratio). *(R.K. Marya, et al, Indian J Physiol Pharmacol 1991 Jul;35(3):170-4)*

Vitamin D supplements should be given to all women in the last trimester of pregnancy who cannot have enough sunshine. *(F. Zeghoud, et al,J Gynecol Obstet Biol Reprod (Paris) 1991;20(5):685-90)*

Hypocalcaemia may be an important factor in the cause of focal seizures which may start after even one month of age. *(J. Oki, et al, Brain Dev 1991;13(2):132-4)*

Severe hypocalcaemia, slower increases in body weight gain, and lower apparent calcium, magnesium, and phosphorus balance values were seen in rats fed a low vitamin D diet. *(M.J. Keenan, et al, Ann Nutr Metab 1991;35(6):315-27)*

In a study on rats injected with vitamin D3 on the 10th day pregnancy, supplementation enhanced skeletal growth which involved both organic and inorganic components in pups. *(R.K. Marya, et al, Ann Nutr Metab 1991;35(4):208-12)*

Osteocalcin is vitamin D-dependent in the fetal and neonatal rat. *(J. Verhaeghe, et al, J Dev Physiol 1990 Dec;14(6):311-7)*

In a study of 13,377 infants, if no vitamin D supplements are given to pregnant women, the incidence of hypocalcaemia in newborn infants was greater in winter (7.72%) than in summer (2.63%). After supplementation, the average incidence fell from 5.11 to 1.93%. *(C. Hellouin de Menibus, et al, Bull Acad Natl Med 1990 Oct;174(7):1051-9; discussion 1059-60)*

In women, vitamin D status has been associated with *in vitro* fertilization (IVF) outcome, features of polycystic ovarian syndrome (PCOS) and endometriosis … Several data converge towards a beneficial effect of vitamin D supplementation in metabolic disturbances in women with PCOS… *(Panagiotis Anagnostis, Spyridon Karras, Dimitrios G. Goulis. 7 January 2013 Volume 67, Issue 3)*

Vitamin D is a versatile signalling molecule, and the male reproductive organs are part of the expanding palette of Vitamin D targets, in addition to the classic effects om bone, calcium and phosphate homeostasis … Improved knowledge of the effects of vitamin D on male reproduction will provide insights concerning the influence of classic bone factors on gonadal function and aid understanding of human production in general. *(Jensen, Martin Blomberg. Nature Reviews. Endocrinology; London 10.3 (Mar 2014): 175-186)*

Given our findings, assessment of Vitamin D status might be considered as a part of routine infertility workup since appropriate assessment of Vitamin D might translate to improved fertility outcome and improved overall health *(Sebiha Ozkan, Sangita Jindal, Keri Greenseid, Jun Shu, Gohar Zeitilian, Cheryl Hickmon, Lubna Pal. September 2010. Volume 94, Issue 4, Pages 1314-1319)*

Alarming findings that populations with the greatest physiological needs for vitamin D, such as pregnant women, neonates, children and adolescents are also at highest risk for vitamin D deficiency *(McCullough, 20007; Alemzadeh et al. 2008; Kovacs 2008)*

Maternal vitamin D deficiency is likely to affect the fetus and the health of the newborn *(Janelle Luk, Saioa Torrealday, Genevieve Neal Perry, Lubna Pal. Human Reprod (2012) 27 (10): 3015-3027)*

In a study of seasonal variation in the hypertensive disorders of pregnancy in Denmark, of the 50 665 women included, 8.5% were diagnosed with a hypertensive disorder of pregnancy. The overall tendency was towards increasing risk when conceiving during spring and early summer, peaking midsummer, and subsequently decreasing steadily during late summer and fall to reach the nadir by winter. Seasonal variation was found for; gestational hypertension (P = .01); preeclampsia (P = .001) and early-onset preeclampsia (P = .014). The study concluded findings a seasonal variation in the risk of the hypertensive disorders of pregnancy in a large cohort of Danish nulliparous women. The highest risk was seen in women with the estimated date of conception in June and August, that is, during summer. Seasonal variation in vitamin D status may explain this association. *(Rohr Thomsen, C, Brink Henriksen, T, Uldbjerg, N, Milidou, I. Seasonal variation in the hypertensive disorders of pregnancy in Denmark. Acta Obstet Gynecol Scand. 2020; 00: 1– 8)*

Vitamin D is mainly made in the skin following exposure to sunlight but can also be taken in via specific natural or fortified food sources. It is essential for intestinal calcium absorption and thereby bone mineralisation. Deficiency in vitamin D, or low dietary calcium intake, therefore results in defective bone mineralisation causing osteomalacia in children and adults and rickets in growing children. The leading causes of rickets and osteomalacia worldwide are solar vitamin D deficiency and/or nutritional calcium deficiency. Long-standing severe vitamin D deficiency can lead to craniotabes, large fontanelle, leg bowing, stunted growth and obstructed labour. **The deficient state in the infant is almost always acquired from the mother. Therefore, robust antenatal and infant vitamin D supplementation programmes are obligatory to prevent complications. Conversely, lack of programme monitoring and conflicting recommendations can lead to confusion among healthcare professionals and poor uptake in the population. Factors shown to improve adherence to supplementation include universal supplementation of breast- and bottle-fed infants**, monitoring supplementation at antenatal/postnatal healthcare visits, providing information to families at discharge from the neonatal unit and financial family support. *(Dr Suma Uday , Jessica Bowie and Professor Wolfgang Högler. British Journal of Midwifery, May 2020, Vol 28, No 5).*

A series of studies have shown that Vitamin D may help regulate reproduction and trophoblast implantation as well as being critical for placental health. (*Lerchbaum E, et al. European Journal of Endocrinology. 2012;166:765. Ganguly A, et al. Journal of Endocrinology. 2018;236:R93. Tamblyn JA, et al. Journal of Endocrinology. 2015;224:R107*)

Evidence shows that vitamin D maintains placental health during pregnancy. Indeed, the placenta expresses vitamin D receptors and is one of the main sources of calcitriol production outside the kidneys. (*Ganguly A, et al. Journal of Endocrinology. 2018;236:R93 . Tamblyn JA, et al. Journal of Endocrinology. 2015;224:R107)*

Placental vitamin D seems to promote innate immune responses (the part of the immune system that responds rapidly but non-specifically to infection), while suppressing the adaptive (antibody mediated), inflammatory responses that could lead to rejection of the fetus. *(Tamblyn JA, et al. Journal of Endocrinology. 2015;224:R107)*

Gestational vitamin D deficiency was associated with autism-related traits in a large population-based sample. Because gestational vitamin D deficiency is readily preventable with safe, cheap and accessible supplements, this candidate risk factor warrants closer scrutiny. *(Vinkhuyzen AAE, Eyles DW, Burne THJ, Blanken LME, Kruithof CJ, Verhulst F, Jaddoe VW, Tiemeier H, McGrath JJ. Gestational vitamin D deficiency and autism-related traits: the Generation R Study. Mol Psychiatry. 2018 Feb)*

A study concluded that the current UK antenatal supplementation programme fails to protect newborns from vitamin D deficiency, especially those from minority ethnic groups who are at high risk of vitamin D deficiency. Nearly 70% of all newborns and 85% of winter-borns had 25OHD concentrations below 50 nmol/L (20 µg/L). Almost 50% of babies of Black or Asian origin were deficient at birth, which explains their high risk of hypocalcaemic complications and rickets if left unsupplemented. *(Uday S, Naseem S, Large J, Denmeade R, Goddard P, Preece MA, Dunn R, Fraser W, Tang JCY, Högler W. Failure of national antenatal vitamin D supplementation programme puts dark skinned infants at highest risk: A newborn bloodspot screening study. Clin Nutr. 2021 May)*

Iron

Parra BE, Manjarres LM, Gomez AL, Alzate DM, Jaramillo MC. 2005. Assessment of nutritional education and iron supplement impact on prevention of pregnancy anemia. *Biomedica,* **25**(2), 211-9.

'Among fertile women, 20% have iron reserves of ±500 mg, which is the required minimum during pregnancy; 40% have iron stores of 100–500 mg, and 40% have virtually no iron stores. The demand for absorbed iron increases from 0.8 mg/day in early pregnancy to7.5 mg/day in late pregnancy. Dietary iron intake in fertile women is median 9 mg/day, i.e. the majority of women have an intake below the estimated allowance of 12–18 mg/day. Iron absorption increases in pregnancy, but not enough to prevent iron deficiency anaemia in 20% of women not taking supplementary iron. Iron-treated pregnant women have greater iron reserves, higher haemoglobin levels, and a lower prevalence of iron deficiency anaemia than placebo-treated women both in pregnancy as well as postpartum. Furthermore, children born to iron-treated mothers have higher serum ferritin levels than those born to placebo-treated mothers. An iron supplement of 65 mg/day from 20 weeks of gestation is adequate to prevent iron deficiency anaemia. In order to avoid iron deficiency in pregnancy, prophylactic iron supplement should be considered.'

Iron status and iron balance during pregnancy, a critical reappraisal of iron supplementation', *(Acta Obstetricia et Gynecologica Scandinavia, Milman N, Bergholt T, Byg K-E, 1999;78)*

Meier PR, Nickerson HJ, Olson KA, Berg RL, Meyer JA. 2003. Prevention of Iron Deficiency Anemia in Adolescent and Adult Pregnancies. *Clin Med Res,* **1**(1), 29-36

P TH, Nguyen CK, van Beusekom C, Gross R, Conde WL, Ha DK. 2005. Milk fortified with iron or iron supplementation to improve nutritional status of pregnant women: an intervention trial from rural Vietnam. *Food Nutr Bull,* **26**(1), 32-8

Osrin D, Vaidya A, Shrestha Y, Baniya RB, Manandhar DS, Adhikari RK, Filteau S, Tomkins A, Costello AM. 2005. Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. *Lancet,* **365**(9463), 955-62.

Milman N, Bergholt T, Eriksen L, Byg KE, Graudal N, Pedersen P, Hertz J. 2005. Iron prophylaxis during pregnancy -- how much iron is needed? A randomized dose- response study of 20-80 mg ferrous iron daily in pregnant women. *Acta Obstet Gynecol Scand,* **84**(3), 238-47

Aguayo VM, Kone D, Bamba SI, Diallo B, Sidibe Y, Traore D, Signe P, Baker SK. 2005. Acceptability of multiple micronutrient supplements by pregnant and lactating women in Mali. *Public Health Nutr,* **8**(1), 33-7

Thinkhamrop J, Apiwantanakul S, Lumbiganon P, Buppasiri P. 2003. Iron status in anemic pregnant women. *J Obstet Gynaecol Res,* **29**(3), 160-3

Makola D, Ash DM, Tatala SR, Latham MC, Ndossi G, Mehansho H. 2003. A micronutrient-fortified beverage prevents iron deficiency, reduces anemia and improves the hemoglobin concentration of pregnant Tanzanian women. *J Nutr,* **133**(5), 1339-46

Bothwell TH. 2000. Iron requirements in pregnancy and strategies to meet them. *Am J Clin Nutr,* **72**(1 Suppl), 257S-264S.

Beard JL. 2000. Effectiveness and strategies of iron supplementation during pregnancy. *Am J Clin Nutr,* **71**(5 Suppl):1288S-94S

Iron is vital for blood formation, and to help prevent anaemia in both mother and developing child. It is also important to guard the mother against excessive blood loss during pregnancy.

Iron is provided in moderation in PREGNACARE, as an excessive level can be harmful during pregnancy, especially if it is not supplemented with zinc.

Excess levels of iron may contribute to intra-uterine growth retardation, and inhibit the absorption of zinc into the body. *(Jnl Am Dietetic Assn 80: 115-121, Feb 1982)*

Inadequate intake of iron related to diets poor in bioavailable iron is often responsible for iron deficiency before pregnancy, and metabolic adjustments (such as mobilisation of iron stores and increased absorption) are insufficient to meet increasing needs during pregnancy. *(I. Blot, et al, Curr Opin Hematol 1999 Mar;6(2):65-70)*

Iron stores in newborns are related to maternal iron status and the materno-fetal unit is dependent on exogenous iron, which is necessary to prevent iron deficiency in both mothers and infants. *(I. Blot, et al, Curr Opin Hematol 1999 Mar;6(2):65-70)*

It is estimated that 60% of pregnant women worldwide are anaemic. *(K.O. O'Brien, et al, Am J Clin Nutr 1999 Mar; 69(3):509-15)*

In a study of 45 pregnant women, 28 of whom were given 60 mg Fe daily from weeks 10 to 24 of gestation until delivery, absorption of iron was not substantially greater in women with depleted iron reserves. Prenatal iron supplementation is important for meeting iron requirements during pregnancy. *(K.O. O'Brien, et al, Am J Clin Nutr 1999 Mar; 69(3):509-15)*

Brain levels of iron and ferritin protein are highly susceptible to dietary iron deficiency. *(T.M. Hansen, et al, Brain Res Mol Brain*

Res 1999 Mar 5;65(2):186-97)

A study of women receiving prenatal care from public health clinics in West Los Angeles from 1983 to 1986 concluded that despite routine iron supplementation, anaemia still occurs in pregnant women and it can predict a preterm delivery. *(A.M. Siega-Riz, et al, Am J Perinatol 1998;15(9):515-22)*

Iron demand is increased by blood losses and by fast growth which increases the risk of iron deficiency in, among others, pregnant women. *(K. Schumann, et al, J Trace Elem Med Biol 1998 Nov; 12(3):129-40)*

In a study of 57 pregnant women, those with iron intakes in the third trimester of over 200% the recommended level showed lower serum zinc levels and, at a later date, lower mature milk zinc levels then subjects with lower iron intakes. *(R.M. Ortega, et al, Med Clin (Barc) 1998 Sep 19;111(8):281-5)*

The requirements of iron during gestation are very high and it is difficult to meet them, especially in women who go into pregnancy with an exhausted storage of the mineral. *(R.M. Ortega, et al, Nutr Hosp 1998 May-Jun;13(3):114-20)*

In a general population sample of 576 women, an association was found in early pregnancy between high dietary Ca intake and lower Fe stores. *(S. Robinson, et al, Br J Nutr 1998 Mar; 79(3):249-55)*

The first comprehensive recommendations to prevent and control iron deficiency, announced by the Centers for Disease Control and Prevention in the United States in 1998, emphasised the importance of low-dose iron supplementation for pregnant women. *(MMWR Morb Mortal Wkly Rep 1998 Apr 3;47(RR-3):1-29)*

Bone marrow produces red blood cells and hemoglobin in proportion to the increase in plasma volume, provided that there is an adequate iron supply (higher in pregnancy compared to the usual dietary intake). *(F. Cantagallo, et al, Minerva Ginecol 1997 Dec;49(12):571-6)*

In a study of pregnant women receiving folic acid and iron supplements from week 5 to 40, tolerability was defined as excellent. Emphasis was placed on the importance of constant supplementation with folic acid and iron throughout pregnancy to avoid sideropenic anaemia, with considerable benefits in terms of the physical conditions of the pregnant woman, the supply of O2 to the villi, fetal wellbeing and the need to resort to possible blood transfusions in the event of major blood losses at birth. *(F. Cantagallo, et al, Minerva Ginecol 1997 Dec;49(12):571-6)*

During pregnancy, the demands for absorbed iron increase from 0.8 to 7.5 mg/day. Controlled studies show that iron-treated pregnant women have higher serum ferritin levels, i.e. larger iron stores, and higher haemoglobin levels than placebo treated

women. *(N. Milman, et al, Ugeskr Laeger 1997 Oct 6;159(41):6057-62)*

In Denmark, general iron prophylaxis with 60-70 mg ferrous iron daily from 20 weeks of gestation is recommended by the health authorities. *(N. Milman, et al, Ugeskr Laeger 1997 Oct 6;159(41):6057-62)*

In a study of 197 pregnant women selected at week 28 of gestation, 99 received 100 mg elemental Fe daily throughout the remainder of pregnancy. In the iron-supplemented group the prevalence of anaemia and iron deficiency decreased markedly during the last trimester of pregnancy but remained constant in the placebo group. Three months after delivery, serum ferritin concentrations, mean length and Apgar scores in infants of the iron group were significantly higher. The prevalence of anaemia was significantly higher in the placebo group three months after delivery. At delivery, there were no differences between the two groups in cord blood iron variables. *(P. Preziosi, et al, Am J Clin Nutr 1997 Nov;66(5):1178-82)*

In a randomised, double-blind, placebo controlled trial, of 30 women receiving 27 mg of non-heme iron with vitamin C daily during the second half of pregnancy, the number of women with empty iron stores postpartum compared to the start of pregnancy rose from 3% to 27%. In the placebo group the numbers rose from 21% to 52%. *(B. Eskeland, et al, Acta Obstet Gynecol Scand 1997 Oct;76(9):822-8)*

Iron supplementation targeted to pregnant women should cover the full reproductive cycle, from pre-pregnancy to at least the end of lactation instead of only the pregnant women. *(F.E. Viteri, Nutr Rev 1997 Jun;55(6):195-209)*

Entering pregnancy with iron deficiency contributes to the failure of antenatal iron supplementation and pre-pregnancy iron reserves increase the effectiveness of antenatal supplementation. *(F.E. Viteri, Nutr Rev 1997 Jun;55(6):195-209)*

Iron supplementation may have beneficial effects on cerebral function in neonates. *(K. Haram, et al, Tidsskr Nor Laegeforen 1997 Mar 10;117(7):966-9)*

A study of 54 anaemic and 22 non-anaemic pregnant women indicated that the fetus extracted iron in amounts proportional to the levels available in the mother. It was concluded that iron deficiency anaemia during pregnancy adversely affects the iron endowment of the infant at birth. *(P.N. Singla, et al, Acta Paediatr 1996 Nov;85(11):1327-30)*

Insufficient dietary intake of iron during pregnancy can result in iron-deficiency anaemia, which is associated with poor intrauterine growth, higher mortality, premature delivery, low birth weight and increased perinatal infant mortality. *(Allen LH. The American Journal of Clinical Nutrition 2005;81:1206s-1212s)*

As the fetus' needs for iron take precedence over the mother's requirements, these stores are soon depleted and infants born to mothers with anaemia have reduced iron stores. So, babies born to women who were anaemic during pregnancy were between 1.8 and 3.7 times more likely to be anaemic during the 3rd to 5th month of life. *(Allen LH. The American Journal of Clinical Nutrition 2005;81:1206s-1212s)*

Replenishing depleted iron stores from dietary sources alone during pregnancy can be difficult.In one study, women who were not taking iron supplements had virtually no iron in their bone marrow (the site of red blood cell production) by late pregnancy. *(Allen LH. The American Journal of Clinical Nutrition 2005;81:1206s-1212s)*

Maintaining adequate iron stores during pregnancy may reduce the risk of postpartum anaemia. For example, a study from the USA found that 27% of women developed postpartum anaemia. However, 49% of women who were anaemic during the third
trimester developed postpartum anaemia compared with 21% of those who were not anaemic.(*Allen LH. The American Journal of Clinical Nutrition 2005;81:1206s-1212s)*

Zinc

Favier M, Hininger-Favier I. 2005. Zinc and pregnancy, *Gynecol Obstet Fertil,* **33**(4), 253-8

Lastra MD, Saldivar L, Martinez K, Munguia N, Marquez C, Aguilar AE. 2005. Zinc concentrations during mice gestation. *Biol Trace Elem Res*, 105(1-3), 205-14

Bo S, Lezo A, Menato G, Gallo ML, Bardelli C, Signorile A, Berutti C, Massobrio M, Pagano GF. 2005. Gestational hyperglycemia, zinc, selenium, and antioxidant vitamins. *Nutrition,* 21(2), 186-91

Pathak P, Kapil U. 2004. Role of trace elements zinc, copper and magnesium during pregnancy and its outcome. *Indian J Pediatr,* 71(11), 1003-5

Zinc supplementation during pregnancy improved the vitamin A status of mothers and infants postpartum, which indicates a specific role of zinc in vitamin A metabolism. Addition of both beta-carotene and zinc to iron supplements during pregnancy could be effective in improving the vitamin A status of mothers and infants (Dijkhuizen MA, Wieringa FT, West CE, Muhilal. 2004. Zinc plus beta-carotene supplementation of pregnant women is superior to beta-carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr,* 80(5), 1299-307)

Essential for processes such as nucleic acid synthesis, and essential for normal foetal growth. **Zinc deficiency is thought to be one factor contributing to a higher incidence of inborn defects or miscarriage.**

"Plasma zinc levels were significantly lower in the maternal blood of 54 women who gave birth to congenitally malformed infants" *(Zinc Deficiency in Human Reproduction, Acta Med Scand. (Suppl.) 593:1-89, 1986)*

"The most critical early period of foetal development usually precedes pregnancy diagnosis. Hence, early zinc supplementation is vital against early foetal abnormalities." *(Prof.P.Aggett: Dept of Child Health, Univ. of Aberdeen, Mineral & Trace Elements, (MTE), Oct 1985)*

"Eight malformed infants in 234 live births were born to women with significantly lower serum zinc concentrations than found in those mothers with normal infants." *(Effects of Zinc Deficiency on Human Reproduction, Acta Med Scand.(Suppl.) 593:1-89, 1976)*

"Plasma zinc concentrations were significantly lower in the maternal blood of 54 women who had given birth to congenitally malformed infants." *(British Journal of Obstetric Gynaecology, 1982, 89:56-58)*

"Out of 100 births, 10 anencephalic infants were delivered to women with significantly lower plasma zinc levels." *(Cadvar, Arcosy et al, Teratology, 1980, 22:141)*

"A high incidence of malformed infants have been reported in populations known to consume diets with low zinc availability." *(L.E. Sever, Zinc and Human Development: a review, Human Ecology, 1975:3, 43-57)*

"Infection is often associated with a transitory drop in serum zinc concentration." *(New England Journal of Medicine, 1977:296, 1129-1134)*

"Zinc available to the developing foetus is derived largely from the maternal blood...Blood zinc levels are especially important during pregnancy. Adequate serum zinc levels are achieved with a daily intake of 20mg of supplemented zinc, provided the daily iron intake does not exceed 50 to 60mg." *(M.W. Breskin et al, School of Medicine & Child Development, Seattle. Am. Jnl of Clin. Nutr, 38:943-953, Dec 1983)*

"Zinc deficiency during the critical period of brain development can cause deficits in neuropsychological function of infants and children that result in impaired performance in school and subsequent adult life." *(I. Kelman Cohen, MD: et al, JAMA, Feb 19,1973, Vol 223, No. 8)*

"Zinc plays a positive role in the absorption of Folic Acid from the gut." *(Am. Jnl of Clin. Nutr, 31:1984-1987, 1978)*

In a study of 1,295 mothers beginning at week 10-24, those supplemented with 15 mg zinc daily had higher serum zinc concentrations and higher urinary concentrations through pregnancy, as well as higher cord concentrations at delivery than those who did not receive supplements. *(L.E. Caulfield, et al, Am J Clin Nutr 1999 Jun;69(6):1257-63)*

In a study of 405 pregnant women, maternal plasma zinc concentrations and infant birth weights were significantly lower in those with intrauterine growth retardation than in normal growth infants. Mothers selected in this way might benefit from zinc supplementation. *(R. Roungsipragarn, et al, J Med Assoc Thai 1999 Feb;82(2):178-81)*

In a study of 50 women with intrauterine growth retardation (IUGR) compared to 43 controls, the IUGR group had lower zinc levels, thus zinc supplementation during pregnancy is recommended. IUGR implies increased risk of morbidity and mortality of the newborn. *(J. Richter, et al, Cent Eur J Public Health 1999 Feb; 7(1):40-2)*

Increased age of the mother is associated with a decrease in zinc levels in placental tissue. *(J. Richter, et al, Cent Eur J Public Health 1999 Feb; 7(1):40-2)*

In a study of 55 fetuses whose mothers received daily supplements of folate and iron with or without 15mg zinc, fetuses of mothers who received zinc showed fewer episodes of minimal heart rate variability, and had increased heart rate range, an increased number of accelerations, movement bouts, amount of time spent moving, and large movements. Improving maternal zinc status through prenatal supplementation may improve fetal neurobehavioral development. *(M. Merialdi, et al, Am J Obstet Gynecol 1999 Feb;180(2 Pt 1):483-90)*

The requirements for zinc during lactation are greater than those during pregnancy, especially during the early weeks postpartum. *(N.F. Krebs, Am J Clin Nutr 1998 Aug;68(2 Suppl):509S-512S)*

Pretreatment of rat embryos with zinc lessened growth retardation, cleft palates and postpartum mortality, induced by increased oxidative stress, through zinc-mediated induction of metallothionein, an important antioxidant. *(D. Blain, et al, J Nutr 1998 Jul;128(7):1239-46)*

Zinc may play a key role in good immune responses as it is required to activate a thymic hormone which is responsible for cell-mediated immunity. *(E. Mocchegiani, et al, Vet Immunol Immunopathol 1998 Apr 16;62(3):245-60)*

In a study of 73 mothers, those with no delivery complications had significantly higher plasma zinc concentrations than those who delivered by vacuum extractor or by urgent cesarean section, and than mothers whose newborns weighed over the 90th percentile. Even a relative zinc deficiency may negatively potentiate certain obstetric abnormalities in fetal development or in delivery. *(R. Biadaioli, et al, Minerva Ginecol 1997 Sep;49(9):371-5)*

Zinc is essential for normal fetal growth and development and for milk production during lactation. *(E.B. Fung, et al, Am J Clin Nutr 1997 Jul;66(1):80-8)*

In a study of 13 women, fractional zinc absorption increased from 14% preconception to 25% during lactation. The nearly twofold increase in zinc absorption was presumably in response to the demand for zinc to synthesise breast milk. *(E.B. Fung, et al, Am J Clin Nutr 1997 Jul;66(1):80-8)*

Oral zinc supplements might have a beneficial effect over some immune responses in the perinatal stages. *(M.D. Lastra, et al, Arch Med Res 1997 Spring;28(1):67-72)*

In a study of 40 healthy pregnant women, results indicated that high levels of maternal serum zinc at delivery may be related to maternal tissue zinc redistribution that could favour diffusional components of maternal-fetal transfer of zinc. *(C.L. Zapata, et al, Biol Neonate 1997;72(2):84-93)*

Younger mothers aged up to 25 years had higher levels of zinc in breast milk compared to those whose age was greater than 25 years. *(A. Frkovic, et al, Sci Total Environ 1996 Dec 2;192(2):207-12)*

A mild deficiency state of zinc in pregnancy is associated with increased maternal morbidity, abnormal taste sensation, prolonged gestation, inefficient labour, atonic bleeding, and increased risks to the fetus. Marginal zinc intake during pregnancy was associated with increased risk of preterm and very preterm delivery in the US. *(A.S. Prasad, J Am Coll Nutr 1996 Apr;15(2):113-20)*

Zinc supplemented infants demonstrate improved linear growth velocity and maximum motor development scores. *(A.S. Prasad, J Am Coll Nutr 1996 Apr;15(2):113-20)*

Marginal and moderate growth impairment in children as a consequence of inadequate zinc intake has been reported from many developed and developing countries. *(A.S. Prasad, J Am Coll Nutr 1996 Apr;15(2):113-20)*

During pregnancy, moderate zinc deficiency not affecting food intake or weight gain still alters whole-body metabolism of polyunsaturates. *(S.C. Cunnane, et al, Can J Physiol Pharmacol 1995 Sep;73(9):1246-52)*

As few as 4 days of maternal zinc deficiency can produce excess embryonal cell death in rats, and neural crest cells may be particularly sensitive. *(J.M. Rogers, et al, Teratology 1995 Sep;52(3):149-59)*

In a randomised double blind placebo controlled trial of 580 pregnant women with plasma zinc levels below the median given either 25mg zinc or placebo from 19 weeks gestation to delivery, infants in the zinc supplemented group had significantly greater birth weight and head circumference. *(R.L. Goldenberg, et al, JAMA 1995 Aug 9;274(6):463-8)*

Zinc is essential for normal fetal growth and development and for milk production during lactation. *(E.B. Fung, et al, Am J Clin Nutr 1997 Jul;66(1):80-8)*

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greater birth weight and head circumference. *(R.L. Goldenberg, et al, JAMA 1995 Aug 9;274(6):463-8)*

Maternal zinc deficiency may increase the risk of pregnancy loss, preterm delivery, still birth and NTDs. (*Wang H, et al. Scientific Reports. 2015;5:11262*)

Magnesium

Durlach J. 2004. New data on the importance of gestational Mg deficiency. *J Am Coll Nutr,* 23(6), 694S-700S

Groenen PM, van Rooij IA, Peer PG, Ocke MC, Zielhuis GA, Steegers-Theunissen RP. 2004. Low maternal dietary intakes of iron, magnesium, and niacin are associated with spina bifida in the offspring. *J Nutr*, 134(6),1516-22.

Caddell JL. 2001. The apparent impact of gestational magnesium (Mg) deficiency on the sudden infant death syndrome (SIDS). *Magnes Res,* 14(4), 291-303

Longo M, Jain V, Vedernikov YP, Facchinetti F, Saade GR, Garfield RE. 2001. Endothelium dependence and gestational regulation of inhibition of vascular tone by magnesium sulfate in rat aorta. *Am J Obstet Gynecol,* 184(5), 971-8

Magnesium is involved in many metabolic processes, such as the metabolism of carbohydrates and amino acids, and the absorption of other minerals.

Magnesium deficiency has been suggested as one possible cause of cot death: its deficiency is a factor in the release of histamine, which increases the permeability of capillaries, allowing nutrients and oxygen to be lost.

Magnesium supplementation during pregnancy was associated with significantly fewer maternal hospitalisations, a reduction in preterm delivery, and less frequent referral of the newborn to the intensive care unit. The results suggest that magnesium supplementation during pregnancy has a significant influence on foetal and maternal morbidity both before and after delivery.'

Magnesium ions (Mg^{2+}) are pivotal in the transfer, storage, and utilisation of energy. Mg^{2+} regulates and catalyzes some 300 enzyme systems, and the intracellular level of free Mg^{2+} regulates intermediary metabolism, DNA and RNA synthesis and structure, cell growth, reproduction, and membrane structure. Mg^{2+} also has numerous physiological roles including control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vasomotor tone, blood pressure

and peripheral blood flow. *(B.M. Altura, et al, Scand J Clin Lab Invest Suppl 1996;224:211-34)*

Maternal magnesium requirements increase during pregnancy because of the synthesis of the new tissue – both fetal and maternal. Magnesium takes part in almost 300 enzymatic reactions in the human body and regulates membrane permeability and protein bio-synthesis. *(G.O. Ajayi, et al, Clin Exp Obstet Gynecol 1998;25(1-2):64-6)*

The amount of magnesium reabsorbed by the body depends on the magnesium intake and not on magnesium needed. *(G.O. Ajayi, et al, Clin Exp Obstet Gynecol 1998;25(1-2):64-6)*

In a study of 51 pregnant women given low dose (3 g daily) magnesium gluconate from the 28th week of gestation to delivery and 51 controls, 4% of the supplemented women developed pregnancy induced hypertension, compared to 16% of the control group. *(S. Li, et al, Chung Hua Fu Chan Ko Tsa Chih 1997 Oct;32(10):613-5)*

In a study of women with threatened preterm delivery at 23-28 weeks gestation, the second trimester was accompanied by lowered serum concentration of total magnesium. *(J. Wojcicka-Jagodzinska, et al, Int J Gynaecol Obstet 1998 May;61(2):121-5)*

In a study of 26 patients with pregnancy induced hypertension and 27 healthy women late in pregnancy, the peripheral serum and mononuclear cell magnesium in women with pregnancy induced hypertension was significantly decreased. *(Q. Qi, et al, Chung Hua Fu Chan Ko Tsa Chih 1997 Jan;32(1):15-8)*

Magnesium is the element with the second highest concentration in the body and is found almost entirely in the intracellular compartment. The small serum component gives a poor representation of the active, physiologic state of the metal. This state is assessed much better by measuring ionized magnesium in the serum. *(J.C. Marcus, et al, Pediatr Neurol 1998 Apr;18(4):311-4)*

In a study of 97 infants, serum ionized magnesium declined significantly with increasing maturity. This decrease may relate to a greater need for magnesium uptake during earlier gestation, more magnesium-induced vasodilation to maintain adequate blood flow to developing tissues and organs, or immature parathormone function earlier in pregnancy. *(J.C. Marcus, et al, Pediatr Neurol 1998 Apr;18(4):311-4)*

In a study of 15 healthy non-pregnant women, 5 women with uncomplicated pregnancy in the third trimester, and 5 pre-eclamptic women, magnesium inhibited induced platelet activation in a dose-dependent manner. Significant inhibition first occurred at a concentration of 4 mg/dL in normal pregnant women, 6mg/dL in pre-eclamptic women, and 8 mg/dL in non-pregnant women. *(W.L. Leaphart, et al, Obstet Gynecol 1998 Mar;91(3):421-5)*

Magnesium sulphate readily crosses the placenta. *(S.W. Walsh, et al, Am J Obstet Gynecol 1998 Jan;178(1 Pt 1):7-12)*

Magnesium is a natural calcium channel blocker inhibiting vasoconstriction in numerous vascular beds. Magnesium sulphate given prior to birth to pre-eclamptic mothers and mothers in preterm labour has been associated with a decreased incidence of both intraventricular haemorrhage and cerebral palsy. *(L. Stigson, et al, Acta Paediatr 1997 Sep;86(9):991-4)*

In a study of 69 infants born before 32 weeks gestational age, there was an inverse relationship between serum magnesium at birth and gestational age. *(L. Stigson, et al, Acta Paediatr 1997 Sep;86(9):991-4)*

In a study of 38 healthy non-pregnant women, 40 healthy women in the first trimester of uncomplicated pregnancy, and 50 pregnant women with symptoms of threatened abortion, the latter group had relatively decreased serum concentration of magnesium. *(R. Smolarczyk, et al, Ginekol Pol 1997 Jan;68(1):11-6)*

In a study of 31 pregnant women, 9 of whom developed pre-eclampsia, total serum magnesium levels decreased significantly by the second trimester in pre-eclamptic women, compared to normal women. *(C.A. Standley, et al, Obstet Gynecol 1997 Jan;89(1):24-7)*

In a study of 144 normal pregnant patients at different stages of gestation, the percent of ionized magnesium in serum was constant in all groups, while mean magnesium concentrations fell with advancing gestational age. It was hypothesized that mobilization of intracellular or bone stores of magnesium help to maintain serum concentrations, thus placing a stress on magnesium balance. *(S.M. Handwerker, et al, J Am Coll Nutr 1996 Feb;15(1):36-43)*

Since the turn of this century there has been a steady and progressive decline of dietary Mg intake to where much of the Western World population is ingesting less than an optimum RDA. *(B.M. Altura, et al, Scand J Clin Lab Invest Suppl 1996;224:211-34)*

Abundant magnesium and copper may protect the retina from developing retinopathy of prematurity (ROP), a major cause of blindness in very low birthweight preterm infants. *(J.L. Caddell, Magnes Res 1995 Sep;8(3):261-70)*

In a prospective, randomised double-blind study of 73 women with pregnancy-related leg cramps given oral magnesium supplements or placebo for 3 weeks, leg cramp distress decreased in the treated group but did not significantly increase serum magnesium levels, excess magnesium being excreted in urine. *(L.O. Dahle, et al, Am J Obstet Gynecol 1996 Jul;175(1):233-4)*

Magnesium depletion, or relative calcium excess, may predispose to vascular complications of pregnancy. *(M. Bardicef, et al, Am J Obstet Gynecol 1995 Mar;172(3):1009-13)*

In a cross-sectional study of 33 normal pregnant women, 12 women with preeclampsia, 2 women with postpartum eclampsia, and 42 nonpregnant women, normal pregnant women had decreased levels of inorganic magnesium ions compared to nonpregnant women, but preeclamptic women did not. *(S.M. Handwerker, et al, J Reprod Med 1995 Mar;40(3):201-8)*

Howard JM, Davies S, Hunnisett A. 1994. Red cell magnesium and glutathione peroxidase in infertile women--effects of oral supplementation with magnesium and selenium. *Magnes Res,* **7**(1):49-57.

In a study of six lactating, six non-lactating, and seven never pregnant women on a low-magnesium diet, lactating women excreted significantly less urinary magnesium than never pregnant women, apparently to compensate for losses in breast milk. No significant differences were seen in magnesium absorption. *(J.L. Dengel, et al, Am J Clin Nutr 1994 May;59(5):990-4)*

Dietary imbalances such as high intakes of fat and/or calcium can intensify Mg inadequacy, especially under conditions of stress when adrenaline stimulates complexing of magnesium with liberated fatty acids. *(M.S. Seelig, J Am Coll Nutr 1994 Oct;13(5):429-46)*

Iodine

Iodine deficiency during pregnancy adversely affects children's mental development .Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longtidinal Study of Parents and Children (ALSPAC). A study of around 1,000 UK mothers and their children, published has revealed that iodine deficiency in pregnancy may have an adverse effect on children's mental development. The research raises concerns that the iodine status of pregnant women is a public-health issue that needs to be addressed.

The researchers measured the iodine concentration in urine samples taken in the first trimester from 1,040 pregnant women. Following World Health Organisation (WHO) guidelines on recommended concentrations of iodine during pregnancy, they classified women who had an iodine-to-creatinine ratio [1] of less than 150 µg/g as being iodine deficient, and those with a ratio of 150 µg/g or more as iodine sufficient. Over two thirds (67 per cent) of the women fell into the category of less than 150 µg/g.

Mental development of the women's children was assessed by measuring child IQ at age 8 and reading ability at age 9. Adjusting the results for external factors likely to affect these scores, such as parental education and breast-feeding, the researchers found that children of women in the iodine-deficient group were significantly more likely to have low scores (lower quartile) of verbal IQ, reading accuracy, and reading comprehension. Moreover, the lower the mother's concentration of iodine, the lower were the average scores for IQ and reading ability in the children.

According to Professor Rayman, 'Our results clearly show the importance of adequate iodine status during early pregnancy, and emphasise the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient.' *(S C Bath, Colin D Steer, J Golding, P Emmett, M P Rayman. The Lancet 2013 Jul 27;382(9889):331-7. doi: 10.1016/S0140-6736(13)60436-5. Epub 2013 May 22)*

'Because even mild maternal iodine deficiency can affect foetal mental development adversely, adequate iodine status in pregnancy is critically important.'*(Multiple micronutrients in pregnancy and lactation – an overview', Allen LH, American Journal of Clinical Nutrition 2005;81)*

'This study provides preliminary evidence that even mild iodine deficiency during pregnancy can have long-term adverse impacts on foetal neurocognition that are not ameliorated by iodine sufficiency during childhood.

Iodine is essential for neurodevelopment in utero and in childhood, with deficiency being a major cause of preventable intellectual impairment.' *(Hynes KL, Otahal P, Hay I, Burgess JR, The Journal of Clinical Endocrinology & Metabolism 2013;98)*

'Our results show the importance of adequate iodine status during early gestation and emphasise the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.' *(Bath SC, Steer CD, Golding J, Emmett P, Rayman MP, The Lancet 2013;382)*

Iodine plays an important role in brain development. *(Sethi V, Kapil U. 2004. Iodine deficiency and development of brain. Indian J Pediatr, 71(4), 325-9.)*

Shah D, Sachdev HP. 2004. Maternal micronutrients and fetal outcome. *Indian J Pediatr,* 71(11), 985-90.

Moscicka A, Gadzinowski J. 2001. The influence of iodine deficiency during pregnancy of fetal and neonatal development, *Ginekol Pol,* 72(11), 908-16

Delange F. The role of iodine in brain development. *Proc Nutr Soc,* 59(1), 75-9.

Dillon JC, Milliez J. 2000. Reproductive failure in women living in iodine deficient areas of West Africa. *BJOG,* 107**(**5), 631-6

During pregnancy maternal thyroid hormones are of great importance for normal development of the central nervous system of the fetus. Iodine deficiency of the mother can result in an impaired development of the fetal brain. *(P.M. Versloot, et al, Eur J Endocrin 1998 Jun;138(6):713-8)*

Marginal iodine deficiency in rats affects maternal thyroid hormone metabolism, thus influencing the availability of maternal thyroxine for the fetus. *(P.M. Versloot, et al, Eur J Endocrin 1998 Jun;138(6):713-8)*

In a longitudinal prospective cohort study throughout pregnancy of 51 healthy women from Sweden and 28 women from Sudan, the history of iodine availability prior to and during pregnancy seemed to be an important determinant of the mechanism of thyroid gland response to ensure the extra iodine needed by the growing fetus. *(B. Elnagar, et al, Eur J Clin Nutr 1998 May;52(5):351-5)*

In an Irish study of women during 3 trimesters of pregnancy, at delivery, and 6 weeks postpartum, thyroid volume showed a significant increase (maximum 47%) compared to non-pregnant controls. *(P.P. Smyth, et al, J Clin Endocrinol Metab 1997 Sep;82(9):2840-3)*

In a study of 258 mothers and their newborns and 516 controls, thyroid volume was about 30% higher in mothers after delivery compared to controls. It was concluded that in spite of general satisfactory iodine intake in Slovak population, the iodine intake during pregnancy was not satisfactory. *(M. Tajtakova, et al, Endocr Regul 1999 Mar;33(1):9-15)*

In a study of women from a moderately iodine deficient area in Sicily, at delivery about 70% of women showed a critical and transient biochemical hypothyroidism. Mental impairment and neurosenorial and neuromuscular disorders were observed in children born from those women. *(F. Trimarchi, et al, Ann Ist Super Sanita 1998;34(3):315-9)*

Iodine deficiency, even moderate, plays a major role in pregnancy associated goiter development, which is only partly reversible after pregnancy. *(W. Reinhardt, et al, Eur J Med Res 1998 Apr 8;3(4):203-10)*

In a study of 70 women from a mildly iodine deficient area given 50 mcg or 250 mcg iodine supplements daily for 8 months postpartum, supplements were considered safe, and even 50 mcg iodine was very efficient in reducing pregnancy associated increments in thyroid volume. *(W. Reinhardt, et al, Eur J Med Res 1998 Apr 8;3(4):203-10)*

In a study of 347 healthy pregnant women in France during 9 months pregnancy, low iodine intake was associated with reduced circulating thyroid hormone levels and growth of the thyroid gland. Data pointed to the need of an increased iodine supply. *(P. Caron, et al, Thyroid 1997 Oct;7(5):749-54)*

In a study on rats, the uptake of iodide by the fetal thyroid decreased by 50% during marginal iodine deficiency. This can lead to diminished thyroid production, which will have a negative effect on fetal development, especially of the brain. *(P.M. Versloot, et al, Am J Physiol 1997 Dec;273(6 Pt 1):E1121-6)*

In a study on rats, chronic maternal dietary iodine deficiency impaired blood-brain barrier nutrient transport in offspring - the rate limiting membrane transport regulating nutrient supply to the brain. *(Y. Sunitha, et al, Neurochem Res 1997 Jul;22(7):785-90)*

Brain damage associated with thyroid dysfunction is irreversible by birth and related to maternal hypothyroxinemia before mid gestation. *(J.R. Martinez-Galan, et al, J Clin Invest 1997 Jun 1;99(11):2701-9)*

In a study of rats fed a low iodine content diet, there was an impaired maturation of cells involved in neuronal migration in the hippocampus, a region known to be affected in cretinism, at a stage of development equivalent to mid gestation in humans. *(J.R. Martinez-Galan, et al, J Clin Invest 1997 Jun 1;99(11):2701-9)*

In a study of 38 mothers in an area of moderate iodine deficiency receiving 300 mcg potassium iodide daily and 70 controls, newborns of supplemented mothers had a significantly lower thyroid volume. *(K.P. Liesenkotter, et al, Eur J Endocrinol 1996 Apr;134(4):443-8)*

In a randomised double blind trial of 180 pregnant women with excessive thyroid stimulation at the end of the first trimester given either placebo or 100 mcg potassium iodide daily, the alterations in thyroid function associated with pregnancy were markedly improved in the supplemented group. Markers of thyroid stimulation decreased and changes in thyroid volume were minimised. Thyroid volumes of infants born to supplemented mothers were normal at birth. *(D. Glinoer, et al, J clin Endocrinol Metab 1995 Jan;80(1):258-69)*

Study results suggest that impairment to children's intelligence development caused by iodine deficiency during their fetal and infant periods is irreversible. *(L.X. Fu, et al, Chung Hua Yu Fang I Hsueh Tsa Chih 1994 Nov;28(6):330-2)*

50-100 million people in Europe are at risk of iodine deficiency disorders (caused by severe iodine deficiency). The most important target groups from a public health point of view are pregnant mothers, fetuses, neonates, and young infants because the main complication of iodine deficiency disorder is brain damage resulting in irreversible mental retardation. This is the consequence of thyroid failure occurring during pregnancy, fetal and early postnatal life**.** *(F. Delange, Thyroid 1994 Spring;4(1):107-28)*

Iodine is essential for the synthesis of the thyroid hormones thyroxine and triiodothyronine, which regulate numerous essential enzymatic and metabolic processes. As a result, iodine deficiency is associated with multiple disorders, including goitre, impaired mental function, delayed growth and development, and hypothyroidism. (*Leung AM, et al. Endocrinology and Metabolism Clinics of North America. 2011;40:765-777. Chaudhry SH, et al. BMC Pregnancy and Childbirth. 2019;19:75*)

Copper

Gambling L, McArdle HJ. 2004. Iron, copper and fetal development. *Proc Nutr Soc,* 63(4), 553-62

Prohaska JR, Brokate B. 2002. The timing of perinatal copper deficiency in mice influences offspring survival**.** *J Nutr,* **132**(10), 3142-5

Penland JG, Prohaska JR. 2004. Abnormal motor function persists following recovery from perinatal copper deficiency in rats. *J Nutr,* **134**(8), 1984-8

Copper is necessary for a range of processes, including protein and phospholipid synthesis. Of additional importance during pregnancy as diarrhoea in the newborn has frequently been linked to copper deficiency.

`Some aspects of maternal diet influence the risk of primitive neuroectodermal tumour in children. The observed protective effects of folate and multivitamin use in pregnancy are the most intriguing because of their specificity...' *(New Engl J Med, 1993; 329:536-41)*

Studies in rats show that a maternal high-fat diet can potentially aggravate the effects of copper deficiency by further altering fetal copper and iron tissue store due to lipid deposition in the liver. *(O. Ebesh, et al, Biol Trace Elem Res 1999 Feb;67(2):139-50)*

Copper deficiency during embryonic and fetal development can result in numerous gross structural and biochemical abnormalities. These can be contributed to by changes in free radical defence mechanisms, connective tissue metabolism, and energy production. *(C.L. Keen, et al, Am J Clin Nutr 1998 May;67(5 Suppl):1003S-1011S)*

Data support the belief that people respond to diets low in copper similarly to animals, and that if common diets low in copper are consumed regularly during pregnancy, maternal stores of copper will be depleted. *(L.M. Klevay, et al, J Nutr 1996 Sep;126(9 Suppl):2419S-2426S)*

Month-old offspring of rat dams fed a copper deficient diet from pregnancy through weaning had up to 80% reductions in regional brain copper concentrations. Concentrations remained lower than controls even after 5 months copper treatment. Long term neurochemical and behavioural abnormalities persisted after perinatal copper deficiency. *(J.R. Prohaska, et al, J Nutr 1996 Mar;126(3):618-27)*

In a study of one hundred mothers and their newborns, there was significant positive correlation between maternal serum copper levels and newborn cord serum copper levels. *(M. Casanova Bellido, et al, An Esp Pediatr 1996 Feb;44(2):145-8)*

A study in rats chronically fed diets marginally low in copper found that abnormalities in cardiac ultrastructure occurred despite minimal changes in conventional biochemical indicators of copper status. *(R.E. Wildman, et al, Proc Soc Exp Biol Med 1995 Oct;210(1):43-9)*

In a study of 30 women who had taken daily iron-folate supplements since the start of the second trimester, the median serum copper concentration was lower than that in the 27 women who had taken no supplements. *(J Burns, et al, Acta Obstet Gynecol Scand 1993 Nov;72(8):616-8)*

The corpus luteum expresses two enzymes that scavenge superoxide radicals and protect the cells from their toxic activities: copper/zinc superoxide dismutase and manganese-SOD. *(N. Sugino, et al, Biol Reprod 1998 Sep;59(3):599-605)*

In two studies of women with missed abortion (43 and 24 patients) compared to controls (73 normal pregnant or 75 nonpregnant women respectively), serum copper concentrations of the groups with missed abortions were significantly lower than controls. *(B. Marinov, et al, Akush Ginekol (Sofiia) 1997;36(3):11-3)*

In rat dams fed a copper deficient diet, placental uptake of copper was increased, but placenta-fetus transport of copper was not improved. *(R.A. Wapnir, et al, Placenta 1996 Sep;17(7):479-86)*

Abundant magnesium and copper may protect the retina from developing retinopathy of prematurity, a major cause of blindness in very low birthweight preterm infants. Protective antioxidant enzyme activity is reduced in magnesium and copper deficiency. *(J.L. Caddell, Magnes Res 1995 Sep;8(3):261-70)*

Selenium

Postpartum depression is a common complication of childbirth. A randomized, double-blind, placebo-controlled trial on 166 women given prenatal selenium supplementation and then assessed eight weeks following delivery showed that they had an significant increase in mean serum selenium concentration at term and that the mean Edinburgh Postnatal Depression Scale (EPDS) score in the selenium group was significantly lower than that of the control group. These findings suggest that supplementation with selenium during pregnancy might be an effective approach for the prevention of postpartum depression. (N Mokhber et al, J Matern Fetal Neonatal Med, 8th June 2010)

There was evidence of selenium deficiency in women with recurrent miscarriages compared with a control group of women with a good reproductive performance (BJOG. 2001 Oct;108(10):1094-7)

'Selenium plays a significant role in the undisturbed functioning of the reproductive system. Selenium deficiencies may lead to gestational complications, miscarriages and the damaging of the nervous and immune systems of the foetus. A low concentration of selenium in blood serum in the early stage of pregnancy has been proved to be a predictor of low birth weight of a newborn. A deficiency of this element may also cause infertility in men by causing a deterioration in the quality of semen and in sperm motility. For this reason, supplementation in the case of selenium deficiencies in the procreation period of both women and men is of utmost significance.'

'The role of selenium in human conception and pregnancy', Human Reproduction Update, Pieczynska J, Grajeta H, 2010;16

Deficiency of minerals such as magnesium, selenium, copper, and calcium have also been associated with complications of pregnancy, childbirth or fetal development (Br J Nutr. 2001 May;85 Suppl 2:S193-7)

Trafikowska U, Sobkowiak E, Butler JA, Whanger PD, Zachara BA. 1998. Organic and inorganic selenium supplementation to lactating mothers increase the blood and milk Se concentrations and Se intake by breast-fed infants. *J Trace Elem Med Biol,* 12(2), 77-85.

Barrington JW, Lindsay P, James D, Smith S, Roberts A. 1996. Selenium deficiency and miscarriage: a possible link? *Br J Obstet Gynaecol,* 103(2),130-2.

Selenium plays a role in preventing anaemia and the development of pre-eclampsia. There is also evidence that selenium supplementation can help to decrease the incidence of pregnancy induced hypertension and gestational edema. (Obs & Gynae., Vol 6, No8 : August 2001)

Selenium supplement on the pregnant women prevented and decreased the incidence of PIH and gestational edema, and elevated the mother's blood Se level. (Chin Med J. 1994 Nov; 107(11):870-1)

Selenium supplementation with 25 to 50 micrograms selenium per day is advisable and should be considered among other trace elements as a food supplement for pregnant and lactating woman. (Rev Fr Gynecol Obstet. 1990 Jan; 85 (1): 29-33)

Rayman MP, Bode P, Redman CW. 2003. Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom. *Am J Obstet Gynecol,* 189(5):1343-9.

Trafikowska U, Sobkowiak E, Butler JA, Whanger PD, Zachara BA. 1998. Organic and inorganic selenium supplementation to lactating mothers increase the blood and milk Se concentrations and Se intake by breast-fed infants. *J Trace Elem Med Biol,* 12(2), 77-85.

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Selenium supplementation with 25 to 50 micrograms selenium per day is advisable and should be considered among other trace elements as a food supplement for pregnant and lactating woman. (Rev Fr Gynecol Obstet. 1990 Jan; 85 (1): 29-33)

Low blood concentration of selenium in early pregnancy increases the risk of low birth weight (Pieczyńska J, et al. Journal of Trace Elements in Medicine and Biology. 2015;29:31-38)

Pantothenic acid

Blood levels of bound pantothenic acid were lower in the girls during pregnancy and 6 weeks postpartum than in the nonpregnant girls. Infant blood from the umbilical cord was higher in pantothenate than maternal blood but lower than reported for infants of well-nourished women. **Based on these findings, inclusion of 5 to 10 mg pantothenic acid in daily prenatal supplements is indicated.** ***Pregnacare Conception provides 6mg Pantothenic Acid*** (Cohenour, S.C: American Journal of Clinical Nutrition, Vol 25, 512-517)

The authors aimed to examine the relation of the intake of 20 micronutrients with birth weight, placental weight, birth length and head circumference of the offspring. They studied 222 Caucasian women with singleton pregnancies in Boston, USA, diet during pregnancy was ascertained at the 27th gestational week through a validated semi-quantitative food frequency questionnaire, covering also intake of dietary supplements.The results showed that Pantothenic acid, sodium and vitamin E were positively associated with all four birth size parameters. For pantothenic acid the association was statistically significant with respect to birth length, whereas for sodium with respect to head circumference and for vitamin E with respect to birth weight. They concluded that pregnancy intake of pantothenic acid, vitamin E and sodium may be positively related with at least one of the studied birth size parameters. (Lagiou P. et al Eur J Nutr 2005 Feb;44(1):52-9. Epub 2004)

Pantothenic acid nutritional status was evaluated longitudinally in 26 pregnant women (experimental group) during their third trimester of pregnancy and at 2 weeks and 3 months postpartum. Seventeen nonpregnant and nonlactating women (control group) participated at the same time intervals. The dietary pantothenate intake averaged 2.75 mg/1,000 kcal. Average pantothenate blood level of the experimental group was lower than that of the control group. When they did not take pantothenic acid supplements, members of the experimental group had intakes less than the Estimated Safe and Adequate Daily Dietary Intake and lower mean blood values than the members of the control group. **This suggests that pregnant and lactating women need to consume more pantothenate to maintain a blood vitamin level similar to that of nonpregnant women.** (Song WO et al. J am Diet Assoc. 1985 Feb;85(2):192-8.)

The effect of the administration of pantothenic acid (PTA) on valproic acid (VPA)-induced teratogenesis was examined in ICR mice. VPA (300, 400, and 500 mg/kg, s.c.) or PTA (3 x 10, 3 x 100, and 3 x 300 mg/kg, i.p.) was injected on day 8.5 of gestation (plug day = day 0.5). Exencephaly was induced dose dependently by single injections of VPA. Three administrations of PTA alone at any dose levels showed neither embryocidal nor teratogenic effects. In combined treatment experiments, PTA (3 x 300 mg/kg) was injected 1 hr before, immediately before, and 1 hr after VPA administration. The results suggest that PTA reduces the incidence of neural tube defect induced by VPA in mice. (Sato M. et al Teratology. 1995 Sep;52(3):143-8.)

Biotin

Recent studies of biotin status during pregnancy provide evidence that a marginal degree of biotin deficiency develops in a substantial proportion of women during normal pregnancy. Several lines of evidence suggest that although the degree of biotin deficiency is not severe enough to produce the classic cutaneous and behavioral manifestations of biotin deficiency, the deficiency is severe enough to produce metabolic derangements in women and may be teratogenic.(*Mock DM J Nutr Biochem 2005 Jul;16(7):435-7)*

Biotin status commonly decreases during pregnancy and maternal adeficiency may translate into fetal deficiency which can be teratogenic and may cause malformations. (*Zempleni J & Mock DM Proc Soc Exp Biol Med 2000 223(1):14-21)*

Wellman® Conception supporting references

Studies confirm that male sperm counts are declining, and environmental factors, such as pesticides, exogenous estrogens, and heavy metals may negatively impact spermatogenesis. A number of nutritional therapies have been shown to improve sperm counts and sperm motility, including carnitine, arginine, zinc, selenium, and vitamin B-12. Numerous antioxidants have also proven beneficial in treating male infertility, such as vitamin C, vitamin E, glutathione, and coenzyme Q10. Acupuncture, as well as specific botanical medicines, have been documented in several studies as having a positive effect on sperm parameters. A multi-faceted therapeutic approach to improving male fertility involves identifying harmful environmental and occupational risk factors, while correcting underlying nutritional imbalances to encourage optimal sperm production and function. (Male infertility: nutritional and environmental considerations. Green Valley Health, Hagerstown, MD 21742, USA. 2000 Feb;5(1):28-38.)

Lycopene Extract

> Excessive generation of reactive oxygen species (ROS) containing free oxygen radicals has been identified as one of the causes of male infertility. Lycopene is a component of human redox defence mechanism against free radicals. It is found in high concentrations in the testes and seminal plasma and decreased levels have been demonstrated in men suffering from infertility. We evaluated the effect of oral lycopene therapy in men with idiopathic infertility. Beginning March 2000, thirty men with idiopathic non obstructiveoligo/ astheno/ teratozoospermia were enrolled for the trial. All patients were administered 2000mcg of Lycopene, twice a day for three months. Semen analysis was performed at three months and sperm concentration, motility and morphology were evaluated. All patients completed the trial without any complications. Twenty patients (66%) showed an improvement in sperm concentration, sixteen (53%) had improved motility and fourteen (46%) showed improvement in sperm morphology. In cases showing an improvement, the median change in concentration was 22 million/ml, motility 25%and morphology 10%. The improvement in concentration and motility were statistically significant. Baseline sperm concentration less than 5 million/ml was associated with no significant improvement. Higher baseline concentrations were associated with significant improvement and resulted in six pregnancies in 26 patients (23%). Oral Lycopene therapy seems to have a role in the management of idiopathic male infertility. Maximum improvement seems to occur in the sperm concentration (66% cases).Patients without severe oligospermia (sperm density >5 million/ml) may be given a trial of therapy with lycopene. (Department of Urology, All India Institute of Medical Sciences, Ansari Nagar, 110029 New Delhi, India)

Objective: to investigate whether lycopene levels in blood and seminal plasma increase after dietary supplementation with a natural source of the compound, and whether any potential increase of lycopene levels in semen translates

into increased free-radical trapping capacity in the seminal plasma. Methods: reactive oxygen species are detrimental to the health and function of spermatozoa. Semen contains enzymatic and non-enzymatic defence mechanisms to combat such species, and lycopene, a dietary antioxidant, forms part of the non-enzymatic arm. Immuno-infertile men have significantly lower levels of lycopene in their semen, and oral lycopene therapy can improve various seminal variables in idiopathic infertility. Whether this improvement is a direct consequence of increased lycopene levels in semen, resulting in an increased radical scavenging ability, remains unknown. Blood and seminal lycopene levels were measured in healthy volunteers, using high-performance liquid chromatography, before and after a period of dietary supplementation. The antioxidant capacity of seminal plasma was also assayed to determine if supplementation results in a measurable increase in seminal radical scavenging ability.
Results: there were statistically significant increases in blood and seminal plasma lycopene levels after dietary supplementation. The increase in seminal and blood lycopene levels showed a strong positive correlation ($r = 0.84$, $P < 0.05$). There was no measurable increase in the total radical scavenging capacity of semen.
Conclusion: this study confirms the presence of lycopene in human semen, the levels of which can be significantly increased after dietary supplementation with a natural source of lycopene. (Goyal, A., Chopra, M., Lwaleed, B.A., Birch, B. and Cooper, A.J. (2007) The effects of dietary lycopene supplementation on human seminal plasma. *BJU International*, 99, (6), 1456-1460.)

Lycopene, a principle phytochemical pigment responsible for the bright red color in tomatoes, is being extensively studied for its potent anti-oxidant and anti-cancerous properties. Now, two studies presented at the 64th Annual Meeting of the American Society for Reproductive Medicine, San Francisco (November 8-12, 2008) suggested that the plant antioxidant protects sperms and eggs from damage caused by oxidative stress, indicating a potential positive impact on the reproductive cells.
In order to examine the anti-oxidative effect of lycopene on sperms, Libman J and colleagues from McGill University, Quebec, Canada, conducted an experimental study, wherein fresh sperm samples isolated from fertile sperm donors were pretreated in solutions with and without lycopene. The samples were then subjected to hydrogen peroxide to induce DNA damage. It was noted that sperms samples treated with lycopene solution sustained less genetic damage when compared to the control samples, suggesting the positive impact of lycopene against oxidative stress-induced damage.
Another study presented at the meeting reported the antiadhesion effects of lycopene. Adhesions, fibrous bands formed during the process of healing after surgery, is one of the common causes of tubular dysfunction, which leads to infertility. Since increased oxidative stress is also known to play an important role in adhesion formation, Dbouk T, et al. from the Wayne State University, Detroit, Michigan, investigated the effect of lycopene on adhesion development. On treatment of adhesive tissue samples with lycopene, it was shown that the antioxidant significantly reduces the expression of proteins associated with adhesions.
Earlier, Mohanty, et al. (*Indian Journal of Urology*, 2001) had conducted a study to investigate whether lycopene was effective in managing idiopathic oligoasthenospermia, a condition associated with low sperm count and motility, and accounting for about 24% of all male infertility. Fifty patients with idiopathic oligoasthenospermia were administered with 8mg of lycopene (Lycored) daily, until significant improvement in sperm counts or pregnancy was achieved. Following regular follow-up for a period of one year, study results documented a 36% pregnancy rate, with significant improvement in sperm count (70%), functional sperm concentration (60%), sperm morphology (38%), sperm motility (54%) and sperm motility index (46%). From the findings, researchers suggested that lycopene has a distinct role in the management of idiopathic oligoasthenospermia.
The presence of excess reactive oxygen species (ROS), resulting from oxidative stress status (OSS) in ejaculates, is considered to be one of the major causative factors of sperm damage, sluggish motility, and low sperm count, leading to idiopathic male infertility. Earlier studies have indicated that 40%-80% of men with infertility have high levels of seminal free oxygen radicals.
Several researches have documented significant anti-inflammatory and anti-coagulant activities of lycopene. Furthermore, lycopene is also associated with reduced risk of macular degenerative disease, serum lipid oxidation and cancers of skin, bladder, lung, ovary and cervix. In addition to other beneficial properties of the plant anti-oxidant, the current evidence suggesting the protective effect of lycopene on germ cells, could serve as a promising intervention to oxidative stress-associated infertility problems. (Lycopene Good for Sperm and Eggs. HIGHLIGHTS FROM THE 64th ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE. Press Release. *American Society for Reproductive Medicine*. Last accessed Nov 13, 2008. Mohanty NK, Kumar S, Jha AK, Arora RP. Management of idiopathic oligoasthenospermia with lycopene. *Indian Journal of Urology*. 2001;18(1):57-61.)

A number of population studies have found a strong correlation between high blood levels of insulin-like growth factor-I (IGF-1) and increased risk of colon, prostate and breast cancer. New research suggests lycopene supplementation may provide some protection by significantly lowering IGF-1. (Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, Giovannucci E. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 2005 Apr;14(4):850-5.)

An optimal intake of lycopene is essential for men. This important nutrient acts as an antioxidant and helps to protect against certain forms of cancer, namely prostate cancer. (Nkosi CZ et al. Effect of pumpkin seed (Cucurbita pepo) protein isolate on the activity levels of certain plasma enzymes in CCl4-induced liver injury in low-protein fed rats. Phytother Res. 2005 Apr;19(4):341-5.)

Maca Extract

Much of the evidence for maca comes from animal studies. In one study in rats, use of maca enhanced male sexual function. (Cicero AF, Piacente S, Plaza A, et al. Hexanic Maca extract improves rat sexual performance more effectively than methanolic and chloroformic Maca extracts. *Andrologia*. 2002;34:177-179.)

In one small 12-week, double-blind, placebo-controlled study, use of maca at 1,500 mg or 3,000 mg increased male libido. (Gonzales GF, Cordova A, Vega K, et al. Effect of *Lepidium meyenii* (Maca) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia*. 2002;34:367.)

Another study found that 4 months of maca use increased sperm count and sperm function. (Gonzales GF, Cordova A, Gonzales C, et al. *Lepidium meyenii* (Maca) improved semen parameters in adult men. *Asian J Androl*. 2002;3:301-303.)

A dose–response study was performed to determine the effect of 7 days oral administration of an aqueous lyophilized extract of Maca at 0.01–5 g/kg (corresponding to 0.022–11 g dry hypocotyls of Maca/kg) on body and different organ weights, stages of the seminiferous tubules, epididymal sperm count and motility, and serum testosterone and estradiol levels in rats. In doses up to 5 g extract/kg, no toxicity was observed. Almost all organ weights were similar in controls and in the Maca extract-treated groups. Seminal vesicles weight was significantly reduced at 0.01 and 0.10 g extract/kg. Maca increased in length of stages VII–VIII of the seminiferous tubules in a dose–response fashion, with highest response at 1.0 g/kg, while caput/corpus epididymal sperm count increased at the 1.0 g dose. (Dose–response effects of *Lepidium meyenii* (Maca) aqueous extract on testicular function and weight of different organs in adult rats; Volume 98, Issues 1-2, 8 April 2005, Pages 143-147)

Numerous animal studies show that maca extracts can increase sex drive and improve fertility. (Cicero AF, Piacente S, Plaza A, et al. Hexanic maca extract improves rat sexual performance more effectively than methanolic and chloroformic maca extracts. *Andrologia* 2002;34:177–9. Gonzales GF, Ruiz A, Gonzales C, et al. Effect of Lepidium meyenii (maca) roots on spermatogenesis of male rats. *Asian J Androl* 2001;3:231–3. Ruiz-Luna AC, Salazar S, Aspajo NJ, et al. Lepidium meyenii (maca) increases litter size in normal adult female mice. *Reprod Biol Endocrinol* 2005;3:16.)

Preliminary studies have shown that maca can increase libido in healthy men. (Gonzales GF, Cordova A, Vega K, et al. Effect of Lepidium meyenii (maca) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia* 2002;34:367–72.)

Healthy men who take maca have also been shown to have increased semen volume, increased sperm counts, and enhanced sperm motility. (Gonzales GF, Cordova A, Gonzales C, et al. Lepidium meyenii (maca) improved semen parameters in adult men. *Asian J Androl* 2001;3:301–3.)

Pine Bark Extract

Pine bark is a rich source of proanthocyanidins (OPCs), known to be potent antioxidants with many benefits associated with circulatory health – such as helping venous insufficiency and vascular constriction. OPCs are 50 times more potent as antioxidants than vitamin E or C and are protective against both fat and water soluble free radicals. Improvements in blood flow and peripheral circulation can assist male reproductive function. (M. Murray. Encyclopedia of Nutritional Supplements. 1996 M. Murray and J. Pizzorno. Male infertility. P.1377-1386. Textbook of Natural Medicine. Second edition. 1999 Sinclair S. Male infertility: nutritional and environmental considerations. Altern Med Rev. 2000 Feb;5(1):28-38.)

Octacosanol

Octacosanol, a waxy substance found in wheat germ oil, has been investigated as an ergogenic agent. Preliminary studies have suggested that octacosanol improves endurance, reaction time, and other measures of exercise capacity (Cureton TK. The physiological effects of wheat germ oil on humans. In: *Exercise*. Illinois: Charles C Thomas, 1972, 296–300.)

Long-term trials in humans using amounts up to 20 mg per day have not shown any negative effects (Pons P, Rodriguez M, Robaina C, et al. Effects of successive dose increases of policosanol on the lipid profile of patients with type II hypercholesterolaemia and tolerability to treatment. *Int J Clin Pharm Res* 1994;14:27–33.)

A study was carried out using 33 male student athletes .Of these, 20 students were used as controls and 13 consumed two "paks" daily (each "pak" contained 29 supplements, including 2,000µg of octacosanol). After eight weeks, all the supplemented subjects showed a decrease in body fat compared to only one in the control group. The supplemented subjects also showed a significant increase in muscle girth measurements, indicating the formation of lean body mass. (Cockerill DL, Bucci LR. Increases in muscle girth and decreases in body fat associated with a nutritional supplement program. Chiro Sports Med 1987;1:73-6.)

An experimental procedure carried out on mice showed that octacosanol enhanced swimming endurance, possibly by converting lipids into energy (Shimura S, Hasegawa T, Takano S, Suzuki T. Studies on the effect of octacosanol on motor endurance in mice. Nutr Rep Int 1987;36:1029-38.)

Inositol

Some preliminary results of studies on high dose inositol supplements show promising results for people suffering from problems such as bulimia, panic disorder, obsessive-compulsive disorder, and unipolar and bipolar depression (Nick, Gina L. (2004). "Inositol as a treatment for psychiatric disorders: a scientific evaluation of its clinical effectiveness". *Townsend Letter for Doctors and Patients* (October). http://findarticles.com/p/articles/mi_m0ISW/is_255/ai_n6211958. Retrieved on 2008-05-24.)

Studies from *in vitro* experiments, animal studies, and limited clinical experiences, claim that inositol may be used effectively against some types of cancer. (jn.nutrition.org)

L-Glutathione

Aside from being a powerful antioxidant booster and system detoxifier, glutathione helps produce, protect and repair deoxyribonucleic acid - DNA. In this protective role, glutathione boosts the immune system, thereby helping to power immune response and preventing the growth of cancerous cells. (Bounous G, Molson J. Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome. Med Hypothesis 53;(4): 347-349. Sen CK. Nutritional biochemistry of cellular glutathione. Nutr Biochem 1997;8:660-72.)

Boosting glutathione levels have been shown to boost sperm count in infertile men. (Lenzi A, Culasso F, Gandini L, et al. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 1993;8:1657-62.)

Declines in glutathione levels are associated with ageing, and studies have shown that adults who took glutathione had better health than those who did not. (Julius M, Lang C, Gleiberman L, et al. Glutathione and morbidity in a community-based sample of elderly. J Clin Epidemiol 1994;47:1021-6.)

L-Arginine

Arginine, an amino acid found in many foods, is needed to produce sperm. Research, most of which is preliminary shows that several months of L-arginine supplementation increases sperm count, quality and fertility. (De Aloysio D, Mantuano R, Mauloni M, Nicoletti G. The clinical use of arginine aspartate in male infertility. *Acta Eur Fertil* 1982;13:133–67. Tanimura J. Studies on arginine in human semen. Part II. The effects of medication with L-arginine-HCl on male infertility. *Bull Osaka Med School* 1967;13:84–9. Scibona M, Meschini P, Capparelli S, et al. L-arginine and male infertility. *Minerva Urol Nefrol* 1994;46:251–3. Schacter A, Goldman JA, Zukerman Z. Treatment of oligospermia with the amino acid arginine. *J Urol* 1973;110:311–3. Schacter A, Friedman S, Goldman JA, Eckerling B. Treatment of oligospermia with the amino acid arginine. *Int J Gynaecol Obstet* 1973;11:206–9.)

Arginine participates in protein synthesis in cells and tissues. It is essential for the synthesis of urea, creatine, creatinine, and pyrimidine bases. It also strongly influences hormonal release and has an important role in vasculature dynamics, participating in the synthesis of nitric oxide (NO). (Division of Endocrinology, Department of Internal Medicine, University of Turin, Turin, Italy, 10.1081/E-EDS-120022067)

Siberian Ginseng Extract

Siberian ginseng is popular for invigorating and fortifying the body. It appears to boost energy levels in people suffering from acute or constant exhaustion. (Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytother Res. 2005 Oct;19(10):819-38.)

Siberian ginseng may be useful in preventing female infertility. Males may experience an increased sperm count. Animal studies indicate that the herb can even boost testosterone levels and thus help reverse certain cases of male impotence. (Salvati G, Genovesi G, Marcellini L, Paolini P, De Nuccio I, Pepe M, Re M. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. Panminerva Med. 1996 Dec;38(4):249-54.)

Scientists have been able to show that Siberian ginseng has a cytotoxic (cell killing) effect on some cancer cell lines in laboratory studies. (Yu CY, Kim SH, Lim JD, Kim MJ, Chung IM. Intraspecific relationship analysis by DNA markers and in vitro cytotoxic and Antioxidant activity in Eleutherococcus senticosus. Toxicol In Vitro. 2003 Apr;17(2):229-36.)

Historically, the Chinese have found Siberian ginseng to be effective in suppressing colds and flu. The herb's immune-enhancing powers may play a role. Recent studies have found that herbal preparations including Siberian ginseng is a helpful adjunctive treatment to conventional therapies for upper respiratory tract infections. Other studies have also shown it to benefit sinusitis. (Narimanian M, Badalyan M, Panosyan V, Gabrielyan E, Panossian A, Wikman G, Wagner H. Randomized trial of a fixed combination (KanJang) of herbal extracts containing Adhatoda vasica, Echinacea purpurea and Eleutherococcus senticosus in patients with upper respiratory tract infections. Phytomedicine. 2005 Aug;12(8):539-47. Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL, Panossian AG, Wikman G, Wagner H. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine. 2002 Oct;9(7):589-97.)

Co-enzyme Q10

Supplements of co-enzyme Q10 (CoQ10) may improve the motility and density of sperm in infertile men, according to a new study using Kaneka's ingredient.
The statistically significant but modest results suggest that CoQ10 may have "potential clinical applications in infertile men", wrote Mohammad Reza Safarinejad from Shahid Beheshti University in Tehran, Iran in the peer-reviewed Journal of Urology.
The researcher called for further prospective studies to evaluate if CoQ10 supplementation may play a role in achieving pregnancy in infertile couples.
CoQ10 has properties similar to vitamins, but since it is naturally synthesized in the body it is not classed as such. With chemical structure 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, it is also known as ubiquinone because of its 'ubiquitous' distribution throughout the human body.
The coenzyme is concentrated in the mitochondria - the 'power plants' of the cell - and plays a vital role in the production of chemical energy by participating in the production of adenosince triphosphate (ATP), the body's co-called 'energy currency'.
A role beyond the mitochondria is also acknowledged, with CoQ10 acting as a potent antioxidant. The coenzyme plays an important role in preserving levels of vitamin E and vitamin C.
There is an ever-growing body of scientific data that shows substantial health benefits of CoQ10 supplementation for people suffering from angina, heart attack and hypertension. Clinical trials have also reported benefits for cardiomyopathy and congestive heart failure.

Study details
Sperm quality has been linked to the level of oxidative stress, and in order to test if CoQ10 levels might beneficially effect sperm quality, Safarinejad recruited 212 infertile men and randomly assigned them to receive a daily CoQ10 supplement (300 mg, Kaneka, Japan) or placebo for 26 weeks. This was followed by 30 weeks with no intervention.
The Tehran-based researchers reported a significant improvement in both sperm density and motility following supplements of the coenzyme. A positive association was also found with regards to sperm count. Further analysis showed an increase in the percent of normal forms of sperm, added Safarinejad.
Finally, an increase in the acrosome reaction of over 100 per cent was observed in the CoQ10 group, compared to a 1 per cent increase in the placebo group. The acrosome reaction aids in egg penetration, and subsequently fertilisation.
"Coenzyme Q10 supplementation resulted in a statistically significant improvement in certain semen parameters," wrote Safarinejad. "However, further studies are needed to draw a final conclusion and evaluate the effect of coenzyme Q10 supplementation on the pregnancy rate." (Source: The Journal of Urology, Volume 182, Issue 1, Pages 237-248 "Efficacy of Coenzyme Q10 on Semen Parameters, Sperm Function and Reproductive Hormones in Infertile Men" Authors: M.R. Safarinejad)

Coenzyme Q10 (CoQ10) is a nutrient used by the body in the production of energy. While its exact role in the formation of sperm is unknown, there is evidence that as little as 10 mg per day (over a two-week period) will increase sperm count and motility. (Tanimura J. Studies on arginine in human semen. Part III. The influences of several drugs on male infertility. *Bull Osaka Med School* 1967;13:90–100.)

L-Carnitine Tartrate

There is a statistically significant, positive correlation between L-carnitine and the number of spermatozoa and the percentage of motile spermatozoa in the human male.' (Matalliotakis I, et al, L-carnitine levels in the seminal plasma of fertile and infertile men: correlation with sperm quality, Department of Obstetrics and Gynecology, University Hospital, Heraklion, Crete, Greece.)

L-carnitine is a substance made in the body and also found in supplements and some foods (such as meat). It appears to be necessary for normal functioning of sperm cells. In preliminary studies, supplementing with 3–4 grams per day for four months helped to normalize sperm motility in men with low sperm quality. (Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. *Andrologia* 1994;26:155–9. Vitali G, Parente R,

Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. *Drugs Exp Clin Res* 1995;21:157–9.)

Carnitine is concentrated within the epididymis and contributes directly to the energy supply required by sperm for maturation and motility. (Sinclair S. Male infertility: nutritional and environmental considerations. *Altern Med Rev.* 2000;5:28–38.)

Treatment with carnitine or acetylcarnitine (1.0–2.0 g/day) increases the number and motility of sperm, and the number of spontaneous pregnancies. (Agarwal A, Nallella KP, Allamaneni SS, Said TM. Role of antioxidants in treatment of male infertility: an overview of the literature. *Reprod Biomed Online*. 2004;8:616–627.)

Growing, if not entirely consistent evidence, suggests that various forms of the supplement L-carnitine may improve sperm function and thereby provide benefit in male infertility (Loumbakis P, Anezinis P, Evangeliou A, et al. Effect of L-carnitine in patients with asthenospermia [abstract]. *Eur Urol.* 1996;30(suppl 2):255. Muller-Tyl E, Lohninger A, Fischl F, et al. The effect of carnitine on sperm count and sperm motility [translated from German]. *Fertilitat.* 1988;4:1-4. Micic S, Lalic N, Nale DJ, et al. Effects of L-carnitine on sperm motility and number in infertile men [abstract]. *Fertil Steril.* 1998;70(3 suppl 1):S12. Vicari E. Effectiveness of a short-term anti-oxidative high-dose therapy on IVF program outcome in infertile male patients with previous excessive sperm Radical Oxygen Species production persistent even following antimicrobials administered for epididymitis: preliminary results. In: International Meeting on Infertility and Assisted Reproductive Technology; June 11-14, 1997; Porto Cervo, Italy. Vicari E, Cerri L, Cataldo T, et al. Effectiveness of single and combined antioxidant therapy in patients with astheno-necrozoospermia from non-bacterial epididymitis: effects after acetyl-carnitine or carnitine-acetyl-carnitine. Presented at: 12th National Conference, Italian Andrology Association; June 9-12, 1999; Copanello, Italy. Campaniello E, Petrarolo N, Meriggiola MC, et al. Carnitine administration in asthenospermia. Presented at: 4th International Congress of Andrology; May 14-18, 1989; Florence, Italy. Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. *Andrologia.* 1994;26:155-159. Vitali G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. *Drugs Exp Clin Res.* 1995;21:157-159. Moncada ML, Vicari E, Cimino C, et al. Effect of acetylcarnitine treatment in oligoasthenospermic patients. *Acta Eur Fertil.* 1992;23:221-224.)

In one double-blind study, 60 men with abnormal sperm function were given either carnitine (as L-carnitine 2 g/day and acetyl-L-carnitine 1 g/day) or placebo for 6 months.[34] The results showed significant improvement in sperm function in the treated group as compared to the placebo group. (Lenzi A, Sgro P, Salacone P, et al. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril.* 2004;81:1578-1584.

Citrus Bioflavonoids

Basic life processes are affected by flavonoids such as immune mechanisms, inflammation, cancer cellular differentiation, atherosclerosis, metabolism, heat shock protein synthesis and possibly aging. There is a body of evidence that the flavonoids possess potentially health promoting effects.*(Pharmaceutical News, p.6-8, Vol. 1, No. 3, 1994)*

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described. It is estimated that humans ingest a few hundred milligrams per day. The intake of flavonols and flavones, which are subclasses of flavonoids, has been inversely associated with subsequent coronary heart disease in most prospective studies. *(P.C. Hollman, et al, Food Chem Toxicol 1999 Sep-Oct;37(9-10):937-42)*

Flavonoids are a group of phenolic compounds found in fruit and vegetables, which are known to have antioxidant properties. *(L. Yochum, et al, Am J Epidemiology 1999 May 15;149(10):943-9)*

A standardized extract composed of a mixture of flavonoids has strong free radical-scavenging activity against reactive oxygen and nitrogen species, and is able to protect endogenous vitamin E and glutathione from oxidative stress. It is also able to modulate the metabolism of nitric oxide, which suggests potential applications in immune and circulatory disorders as well as in neurodegenerative disease. It can bind to proteins, altering their structure and

thereby modulating the activity of key enzymes and proteins involved in metabolic pathways. Finally, it has been reported to have cardiovascular benefits, such as vasorelaxant activity, angiotensin-converting enzyme inhibiting activity, and the ability to enhance the microcirculation by increasing capillary permeability. *(L. Packer, et al, Free Radic Biol Med 1999 Sep;27(5-6):704-24)*

Vitamin A

Urinary excretion of norepinephrine and epinephrine significantly increased in vitamin A depleted rats. It also caused a significant increase in norepinephrine turnover in heart and spleen. (K. Nakano, et al, J Nutr Sci Vitaminol (Tokyo) 1984 Apr30(2):163-70)

Study results suggest that vitamin A depletion causes derangement of the neurosympathetic system in rats, making them unable to respond appropriately to stress. Alternately, vitamin A depletion may itself be a stress so that the animals are already in a state of maximal response. (R. Mizutani, et al, J Nutr 1982 Dec;112(12):2205-11)

Vitamin A, its analogues and its metabolites function in vision, cell differentiation, embryogenesis, the immune response, reproduction and growth. (JS Garrow, WPT James, A Ralph, Human Nutrition and Dietetics, 10th Edition, Chapter 13 p230-231, Churchill Livingstone.)

In vitamin A deficiency, both specific and non-specific protective mechanisms are impaired, namely: the humoral response to bacterial, parasitic and viral infections; cell-mediated immunity; mucosal immunity, natural killer cell activity and phagocytosis. The immune responses to certain antigens in vitamin A depleted children are enhanced by vitamin a supplementation. (A C Ross, U G Hammerling. Retinoids and the immune system (1994). In Sporn M B, Roberts A B, Goodman D S (eds) The retinoids: biology, chemistry and medicine, 2nd edition Raven Press, New York, pp 521-543)

Vitamin A was termed the 'anti-infective' vitamin based on the increased number of infections noted in vitamin A deficient animals and humans. (A Sommer, K P West Jr, Vitamin A deficiency-health, survival and vision. Oxford University Press, Oxford 1996)

Another major function of Vitamin A is in cell differentiation. The recent discovery of two sets of retinoic acid receptors, the RAR and RXR, has clarified in large part the molecular action of vitamin A in this process. (P Chambon FASEB Journal (1996) 10:940-954 and D J Mangelsdorf et al. The retinoid receptors. In Sporn M B, Roberts A B, Goodman D S (eds) The retinoids: biology, chemistry and medicine, 2nd edition Raven Press, New York, pp 319-349.

Vitamin D3

We performed experiments to determine whether treatment with vitamin D or 1,25-dihydroxycholecalciferol could reverse male infertility caused by vitamin D deficiency. Additionally, an attempt was made to distinguish between a direct and an indirect effect of 1,25-dihydroxycholecalciferol on reproductive tissue. Vitamin D-deficient male rats with impaired fertility were treated with vitamin D and 1,25-dihydroxycholecalciferol for 3 wk, then mated. Secondly, vitamin D-deficient male rats were made normocalcemic by increasing dietary calcium, and their fertility was compared with that of vitamin D-deficient, hypocalcemic rats. The fertility of male rats was restored by treatment with either vitamin D or 1,25-dihydroxycholecalciferol. However, fertility was also restored in vitamin D-deficient animals by feeding them a diet supplemented with high levels of calcium. These results indicate that the influence of vitamin D and its active metabolite, 1,25-dihydroxycholecalciferol, on male fertility is indirect. Vitamin D and 1,25-dihydroxycholecalciferol seemed to influence male fertility by acting on classic target tissues and regulating levels of

calcium in reproductive tissues. (Uhland, A M : Kwiecinski, G G : DeLuca, H F. Normalization of serum calcium restores fertility in vitamin D-deficient male rats. J-Nutr. 1992 Jun; 122(6): 1338-44)

Researchers at Fertility First, in Sydney, Australia, were studying sperm to see which ones and how many had damaged DNA, in the hope that it may shed light on why the 800 men enrolled, could not impregnate their partners.

All the men had undergone blood testing, and it was noticed purely by chance that a third of the men had vitamin D and folate deficiencies. A substance known as homocysteine, an amino acid which occurs when the body is toxic through lack of folate and vitamins, was present in the blood. The medical profession already know how important vitamin D and folic acid is to women, and that a lack of these can cause infertility, which is one of the reasons why women are encouraged to take folic acid supplements for three months prior to trying for a baby, but until now they didn't know that the same was true for men. (Vitamin D Deficiency And Infertility Low Vitamin and Folate Levels Have Been Observed In Infertile Men. Joanna Karpasea-Jones Nov 5, 2008)

'Vitamin D is essential for skeletal growth and bone health. Dietary sources in the UK are very limited and oily fish is the only significant source. The major natural source is from skin synthesis following exposure to sunlight. From mid-October to the beginning of April in the UK there is no ambient ultraviolet sunlight of the appropriate wavelength for skin synthesis of vitamin D.

For example, many health professionals and the public may be unaware that the skin cannot synthesise vitamin D from sunlight during winter months in the UK. They may also be unaware that a balanced diet alone will not provide sufficient vitamin D. In addition, they do not know enough about the importance of vitamin D supplements for at risk groups.

A newborn baby's vitamin D status is largely determined by the mother's level of vitamin D during pregnancy. Breastfed infants may need drops containing vitamin D from 1 month of age if their mother has not taken vitamin D supplements throughout pregnancy.

Breast milk is not a significant source of vitamin D.

The current reference nutrient intakes (µg/day) for vitamin D are:

- 8.5 for infants up to 6 months
- 7 for children between 6 months and 3 years
- 10 for women during pregnancy and lactation and adults over 65.

Currently there is no reference nutrient intake for people aged between 4 and 65 years. It is assumed that the action of sunlight on skin will provide adequate vitamin D, except for specific at-risk groups, such as women whose clothing conceals them fully or those confined indoors. ('Dietary reference values for food energy and nutrients for the United Kingdom. Report of the panel on dietary reference values of the Committee on Medical Aspects of food policy' Department of Health.)

At risk groups are currently advised to take a supplement that meets 100% of the reference nutrient intake for their age group (as above). The reference nutrient intake for at risk groups is 10 micrograms/day (1 microgram=40 international units, so 10 micrograms=400 IU).'

'Vitamin D: Increasing supplement use among at-risk groups', National Institute for Health and Care Excellence, Guidance PH56

'We present evidence that vitamin D is involved in female reproduction including IVF outcome (clinical pregnancy rates) and polycystic ovary syndrome (PCOS).

In PCOS women, low 25-hydroxyvitamin D (25(OH)D) levels are associated with obesity, metabolic, and endocrine disturbances and vitamin D supplementation might improve menstrual frequency and metabolic disturbances in those women.

Moreover, vitamin D might influence steroidogenesis of sex hormones (estradiol and progesterone) in healthy women and high 25(OH)D levels might be associated with endometriosis.

In men, vitamin D is positively associated with semen quality and androgen status. Moreover, vitamin D treatment might increase testosterone levels.'

'Vitamin D and fertility: A Systematic Review', Lerchbaum E, Obermayer-Pietsch B, European Journal of Endocrinology 2012; 166

Several animal studies have suggested that vitamin D and the vitamin D receptor (VDR) play a role in male fertility. The mechanism of action in the testis and the interaction with sperm is unknown. The presence of the VDR on sperm has never been demonstrated. The objective of this pilot study was to investigate the presence of the VDR on human sperm.
Methods
A prospective study of sperm collected from 10 fertile men, mean age 33.7 ± 2.2 years, was undertaken. Qualitative analysis for VDR was performed by immunohistochemistry using a monoclonal antibody to human VDR. For comparison of the spatial relationship of the receptor, qualitative analysis of the androgen receptor on sperm was performed. Immunoprecipitation and immunoblotting of total sperm protein lysate using VDR antibodies further characterized the VDR.
Results
Immunohistochemistry demonstrated that the VDR was located predominantly on the head/nucleus of the sperm and mid-piece. Immunoblotting confirmed the presence of the VDR with a molecular weight of 50 kDa in all subjects.
Conclusions
Our results have demonstrated the presence of the VDR on human sperm for what we believe to be the first time. (Vitamin D receptor found in human sperm, Volume 68, Issue 6, December 2006, Pages 1345-1349)

Vitamin E

Vitamin E has shown to increase the motility of sperm and may have a substantial benefit on improved sperm motility and potential increase in fertilization in asthenospermic subjects (men with reduced spermatozoon motility in the semen). In a study of patients with asthenospermia treated with oral vitamin E, eleven out of the 52 treated patients (21%) impregnated their spouses; nine of the spouses successfully ended with normal term deliveries, whereas the other two aborted in the first trimester. No pregnancies were reported in the spouses of the placebo-treated patients. (S. A. Suleiman et al, Lipid Peroxidation and Human Sperm Motility: Protective Role of Vitamin E, Journal of Andrology, 1996; vol. 17, No. 5; 530-537)

In a double-blind, placebo-controlled study of 110 men whose sperm showed subnormal activity, daily treatment with 100 IU of vitamin E resulted in improved sperm activity and increased rate of pregnancy in their partners. (Suleiman SA, Elamin Ali M, Zaki ZMS, et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. *J Androl.* 1996;17:530-537.)

Vitamin E deficiency in animals leads to infertility. (Thiessen DD, Ondrusek G, Coleman RV. Vitamin E and sex behavior in mice. *Nutr Metab* 1975;18:116–9.)

In a preliminary human trial, 100–200 IU of vitamin E given daily to both partners of infertile couples led to a significant increase in fertility. (Bayer R. Treatment of infertility with vitamin E. *Int J Fertil* 1960;5:70–8.)

In a preliminary study, men with low fertilization rates in previous attempts at *in vitro* fertilization were given 200 IU of vitamin E per day for three months.[43] After one month of supplementation, fertilization rates increased significantly, and the amount of oxidative stress on sperm cells decreased. (Geva E, Bartoov B, Zabludovsky N, et al.

The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. *Fertil Steril* 1996;66:430–4.)

A double-blind, randomized, cross-over controlled study by Kessopoulou *et al.* examined 30 men with high ROS production. Three hundred milligrams of vitamin E (the amount found in approximately 2.7 cups of sunflower oil) was supplemented twice daily for 3 months. During the supplementation, there was a significant improvement in the in vitro ability of spermatozoa to bind the zona pellucida of unfertilized oocytes as compared to binding during the 3 months of placebo. (Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russel JM, Cooke ID and Barratt CLR (1995) A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. *Fertil Steril*. 64(4): 825-831.)

A double-blind, randomized study by Suleiman *et al*. in 1996 looked at a group of 87 men with decreased sperm motility (asthenozoospermia). Those who were randomized to receive vitamin E for 6 months (100 mg 3 times daily) had significantly decreased levels of lipid peroxidation product and improved sperm motility as compared to the placebo group. Percent motility in the treated group increased from a mean of 31.1% to 48.9% compared to an increase from 30.6% to 35.9% in the placebo group ($p<0.01$). Furthermore, 21% of treated patients impregnated their partners while no pregnancies were reported in the placebo group. (Suleiman SA, Ali ME, Zaki ZMS, El-Malik EMA and Nasr MA (1996) Lipid peroxidation and human sperm motility: protective role of vitamin E. *J Androl*. 17: 530-537.)

There is some evidence that suggests a relationship between daily antioxidant intake and better semen quality among healthy men. Semen analysis was performed on 97 healthy male volunteers and results were correlated with the results of a dietary assessment questionnaire. Higher levels of vitamin E intake were associated with higher levels of progressive sperm motility. (Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G and Wyrobek AJ (2005) Antioxidant intake is associated with semen quality in healthy men. *Hum Reprod*. 20(4): 1006-1012.)

Recent evidence suggests that oral vitamin E supplementation may also be beneficial in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI, where a single sperm is injected into an ovum). A 2005 meta-analysis concluded that IVF rates were negatively correlated with ROS levels and so decreasing ROS levels in couples undergoing IVF may be useful. A prospective study of IVF rates in 15 males supports this possibility as it found a decrease in lipid peroxidation and an increase in fertilization rate per cycle after 3 months of vitamin E supplementation (200 mg daily). (Geva E, Bartoov B, Zabludovsky N, Lessing JB, Lerner-Geva Liat and Amit A (1996) The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. *Fertil Steril*. 66(3): 430-434.)

Since studies have found that only 8% of US men consume sufficient amounts of vitamin E, it is reasonable to encourage infertile males to maintain adequate dietary intakes of vitamin E through diet or supplements. (Maras JE, Bermudez OI, Qiao N, Bakun PJ, Boody-Alter EL and Tucker KL (2004) Intake of alpha-tocopherol is limited among US adults. *J Am Diet Assoc*. 104(4): 567-75.)

Vitamin C

Vitamin C - a high concentration of the antioxidant vitamin C in semen plays a key role in maintaining the genetic integrity of sperm cells, by preventing oxidative damage to sperm DNA. This might affect sperm quality and increase risk of genetic defects, particularly in populations with low ascorbic acid, such as smokers. In a study of 75 heavy smokers given 200 or 1000 mg vitamin C or placebo daily for one month, treated groups showed improvement in sperm quality. (C.D. Hunt, et al, Am J Clin Nutr 1992;56/1:148-157)

Preliminary studies suggest that vitamin C may improve sperm count and function. (Dawson EB, Harris WA, Rankin WE, et al. Effect of ascorbic acid on male fertility. *Ann N Y Acad Sci.* 1987;498:312-323)

Vitamin C protects sperm from oxidative damage. (Fraga CG, Motchnik PA, Shigenaga MK, et al. Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. *Proc Natl Acad Sci* 1991;88:11003–6.)

Supplementing vitamin C improves the quality of sperm in smokers. (Dawson EB, Harris WA, Teter MC, Powell LC. Effect of ascorbic acid supplementation on the sperm quality of smokers. *Fertil Steril* 1992;58:1034–9.)

When sperm stick together (a condition called agglutination), fertility is reduced. Vitamin C reduces sperm agglutination, and supplementation with 200–1,000 mg per day increased the fertility of men with this condition in a controlled study. (Dawson EB, Harris WA, McGanity WJ. Effect of ascorbic acid on sperm fertility. *Fed Proc* 1983;42:531 [abstr 31403]. Dawson EB, Harris WA, Powell LC. Relationship between ascorbic acid and male fertility. In: Aspects of Some Vitamins, Minerals and Enzymes in Health and Disease, ed. GH Bourne. *World Rev Nutr Diet* 1990;62:1–26 [review]. Dawson EB, Harris WA, Rankin WE, et al. Effect of ascorbic acid on male fertility. *Ann N Y Acad Sci* 1987;498:312–23.)

Thiamin (Vitamin B1)

A mouse model of thiamin-responsive megaloblastic anemia (diabetes mellitus, deafness, megaloblastic anemia) lacking functional Slc19a2 has been generated and unexpectedly found to have a male-specific sterility phenotype. We describe here the characterization of the testis-specific effects of absence of the high-affinity thiamin transporter, Tht1. Null males were found to have hypoplastic testes secondary to germ cell depletion. Morphologic and expression analysis revealed that under conditions of standard thiamin intake, tissues affected in the syndrome (pancreatic beta-cell, hematopoietic cells, auditory nerve) maintained normal function but pachytene stage spermatocytes underwent apoptosis. Under conditions of thiamin challenge, the apoptotic cell loss extended to earlier stages of germ cells but spared Sertoli cells and Leydig cells. Injection of high-dose thiamin was effective in reversing the spermatogenic failure, suggesting that the absence of the thiamin carrier could be overcome by diffusion-mediated transport at supranormal thiamin concentrations. These observations demonstrated that male germ cells, particularly those with high thiamin transporter expression beyond the blood-testis barrier, were more susceptible to apoptosis triggered by intracellular thiamin deficiency than any other tissue type. The findings described here highlight an unexpected and critical role for thiamin transport and metabolism in spermatogenesis. (Male infertility due to germ cell apoptosis in mice lacking the thiamin carrier, Tht1. A new insight into the critical role of thiamin in spermatogenesis)

"Those on high carbohydrate intakes (high in sugar and starch) require higher intakes of thiamin, as do those with a high intake of alcohol, smokers and those subject to excessive stress". (S Davies and A Stewart (1987); Nutritional Medicine: A Drug-Free Guide to Better Family Health; Pan Books; London).

In a study of rats fed diets with differing amounts of protein, and sucrose content inversely related to protein content, protein malnutrition did not alter tissue thiamin concentrations, but decreased transketolase activity in the brain, indicating functional thiamin deficiency. (S.M. Ahmed, et al, J Am Coll Nutr 1988 Jun;7(3):215-21)

Thiamin is a co-factor for enzymes key in bridging aerobic and anaerobic metabolism. One such enzyme, transketolase, catalyzes two of three reactions for entry into a major source of chemical reducing power. Thus, thiamin deprivation is considered a classic model of systemic oxidative stress and is linked with degenerative diseases. In rats, thiamin deficiency produces neurodegeneration with Alzheimer's disease characteristics. (P.H. Frederikse, et al, Biochem Biophys Res Commun 1999 May 19;258(3):703-7)

A study in rats fed ethanol, together with thiamin at a dose equivalent to 15.47mg thiamin daily in humans, for 20 weeks concluded that thiamin megavitamin therapy supports a neuron's carbohydrate metabolism and therefore could be able to prevent or reduce alcohol-induced damages to certain cells in the central nervous system. (S. Wenisch, et al, Z Ernahrungswiss 1996 Sep;35(3):266-72)

Scientific literature confirms that thiamin deficiency can be both predisposing to, and be a consequence of, increased alcohol consumption. In one study, the activity of a marker of a thiamin dependent enzyme decreased 61-79% in the

blood, liver and brain of rats fed 15% ethanol as their only source of drinking fluid for 6 months. Another study showed that thiamin deficiency leads to a prolonged increase of the preferential intake of ethanol solutions in rats. (S.M. Zimatkin, et al, Alcohol Alcohol 1996 Jul;31(4):421-7)

A survey of first-time blood donors in Australia in 1995 revealed a significant prevalence of low red blood cell thiamin concentrations (13%). (C.K. Booth, et al, Am J Clin Nutr 1998 Nov;68(5):1075-80)

Riboflavin (Vitamin B2)

In a study of 6 sedentary to moderately active men with previous biochemical signs of riboflavin deficiency (improved at the start of the study), additional exercise for 18 days between two periods of habitual activity resulted in a significant deterioration in riboflavin status, suggesting an increased demand for the vitamin for selective biochemical functions during exercise. (M.J. Soares, e tal, Br J Nutr 1993 Mar69(2):541-51)

In a study on rats after exercise for 6 or 8 weeks, total riboflavin retention increased in gastrocnemius and soleus muscles. (K.E. Hunter, et al, J Nutr 1987 Feb;117(2):298-304)

In a study of 132 healthy vegetarians age range 25-57 years who had been practicing vegetarianism for 1-22 years, compared to 68 healthy non-vegetarian controls, 24.2% of vegetarians were deficient in vitamin B2, as well as 22.2% of controls. (N. Vudhivai, et al, J Med Assoc Thai 1991 Oct;74(10):465-70)

In a study of young rats fed a diet deficient in folic acid and vitamin B2, haemoglobin concentration as well as haemocrit value and red blood cell count were highest in rats which received replenishing supplementation with the full dosage of both vitamins. (D.Y. Dako, et al, Int J Vitam Nutr Res 1980;50(3):254-60)

Niacin (Vitamin B3)

A study of patients with high-density lipoprotein less than 35 mg/dl and without hypertriglyceridemia showed that niacin supplementation could increase high-density lipoprotein ('good' cholesterol) levels by 16%. (A.C. Sposito, et al, Am J Cardiol 1999 Jan 1;83(1):98-100, A8)

Niacin is effective therapy for lipoprotein regulation and cardiovascular risk reduction. (D.M. Capuzzi, et al, Am J Cardiol 1998 Dec 17;82(12A):74U-81U;discussion 85U-86U)

Niacin is a useful lipid-modifying nutrient because it decreases low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein(a), while at the same time increasing high-density lipoprotein (HDL) cholesterol. (A.C. Goldberg, Am J Cardiol 1998 Dec 17;82(12A):35U-38U;discussion 39U-41U)

Niacin manifests beneficial effects in cardiovascular disease with respect to dyslipidemic states. It lowers low-density lipoprotien (LDL) cholesterol, triglycerides, lipoprotein(a) and increases high-density lipoprotein (HDL). (J.M. Morgan, et al, Am J Cardiol 1998 Dec 17;82(12A):29U-34U;discussion 39U-41U)

Study results demonstrate that niacin supplementation decreases plasma fibrinogen and low-density lipoprotein cholesterol in subjects with peripheral vascular disease. (C.S. Philipp, et al, Am J Cardiol 1998 Sep 1;82(5):697-9,A9)

Niacin has been used for many years to treat hyperlipidemia. It has been shown to reduce coronary death and non-fatal myocardial infarction and, in separate analysis of long-term (15 year) follow-up, all cause mortality. It reduces total cholesterol, low-density lipoprotein cholesterol and triglycerides and increases high density lipoprotein cholesterol. (J.R. Crouse 3rd, Coron Artery Dis 1996 Apr;7(4):321-6)

Vitamin B6

Needed for the production of red blood cells and antibodies, coenzyme in protein, fat and carbohydrate metabolism. Vitamin B6 also plays a vital role in both humeral and cell mediated immunity. *(J. Nat. Cancer Inst. 1987:5, 951)*

Vitamin B6 may play a role in attenuating the rise in plasma growth hormone during exercise. (M.M. Manore, et al, Int J Sport Nutr 1994 Jun;4(2):89-103) In a study of 13 endurance athletes, there was a mean loss of about 1 mg vitamin B6 as a result of a marathon race. (L. Rokitzki, et al, Int J Sport Nutr 1994 Jun; 4(2):154-65)

Studies of norepinephrine content in the brains of rats exposed to stress suggest an antistress effect of vitamin B6. (J.G. Henrotte, et al, Ann Nutr Metab 1992; 36(5-6):313-7)

In a study on monkeys, pretreatment with vitamin B6 resulted in a 20% enhancement of the rate of serotonin formation in the brain, indicating the regulatory role of vitamin B6 on the synthesis of neurotransmitter in vivo, and that vitamin B6 may be important in diseases with deficiencies in neurotransmitter function. (P. Hartvig, et al, J Neural Transm Gen Sect 1995;102(2):91-7)

In a study on 1,149 patients with various peripheral nervous system diseases, after three weeks of treatment with a vitamin B preparation, a positive effect on pain in particular was observed in 69% of the cases. Similar observations were also made for parasthesias and muscular weakness in the legs. (M. Eckert, et al, Fortschr Med 1992 Oct 20;110(29):544-8)

Folacin (Folic Acid)

Increasing folic acid intake for fathering men, may be advantageous in reducing the risk of chromosomal anomalies in their offspring. A study in the association of folate, zinc and antioxidant intake with sperm aneuploidy (abnormal number of chromosomes) in healthy non-smoking men, found that men with high folate intake had lower overall frequencies of several types of aneuploid sperm. (S.S. Young et al, The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men, Human Reproduction 2008 23(5):1014-1022)

Vitamin B12

Vitamin B12 is needed to maintain fertility. Vitamin B12 injections have increased sperm counts for men with low numbers of sperm. (Sandler B, Faragher B. Treatment of oligospermia with vitamin B12. *Infertility* 1984;7:133–8.)

A group of infertile men were given oral vitamin B12 supplements (1,500 mcg per day of methylcobalamin) for 2 to 13 months. Approximately 60% of those taking the supplement experienced improved sperm counts. (Isoyama R, Baba Y, Harada H, et al. Clinical experience of methyl-cobalamin (CH3-B12)/clomiphene citrate combined treatment in male infertility. *Hinyokika Kiyo* 1986;32:1177–83 [in Japanese].)

Abnormalities of motor conduction are part of the changes in vitamin B12 deficiency in addition to the involvement of the sensory nerves. (M.A. Carvalho, et al, Electromyogr Clin Neurophysiol 1996 Jul-Aug;36:163-91)

Vitamin B12 deficiency causes a deficient remethylation of homocysteine and therefore probably contributes to increased homocysteine levels. (B. Regland, et al, Scand J Rheumatol 1997;26(4):301-7)

A study of 6 women and 14 men treated for 14 days with 3 mg vitamin B12 or methylcobalamin (a coenzyme derived from vitamin B12), found that changes in “sleep quality”, “concentration” and “feeling refreshed” showed significant correlation with vitamin B12 plasma levels. It was concluded that vitamin B12 exerts a direct influence on melatonin. Methylcobalamin also had an alerting affect, with a distribution of the sleep-wake cycle toward sleep reduction. (G. Mayer, et al, Neuropsychopharmacology 1996 Nov;15(5):456-64)

A study of patients with normal serum vitamin B12 levels given injections of vitamin B12 found that with higher serum vitamin B12 levels, the patterns of a Multiphasic Personality Inventory test (an objective computerized psychological test to indicate feelings of well-being) were at or closer to ‘normal’. With lower serum vitamin B12 levels, test patterns showed much more emotional distress. (H.L. Newbold, Med Hypotheses 1989 Mar;28(3):155-64)

A study aimed to evaluate whether the availability of vitamin B-12 and folate and the expression or activity of the target enzymes of the remethylation pathway are involved in NTD risk. The study concluded that decreased vitamin

B-12 in liver and cord blood and decreased expression and activity of MS in liver point out the impaired remethylation pathway as hallmarks associated with NTD risk. The study suggested evaluating vitamin B-12 in the nutritional recommendations for prevention of NTD risk beside folate fortification or supplementation. *(Ma'atem B Fofou-Caillierez, Rosa-Maria Guéant-Rodriguez, Jean-Marc Alberto, Céline Chéry, Thomas Josse, Philippe Gérard, Thierry Forges, Bernard Foliguet, François Feillet, Jean-Louis Guéant, Vitamin B-12 and liver activity and expression of methionine synthase are decreased in fetuses with neural tube defects, The American Journal of Clinical Nutrition, Volume 109, Issue 3, March 2019, Pages 674–683)*

Biotin

Biotin is a water-soluble vitamin that acts as an essential step in intermediary metabolism. In humans, biotin deficiency causes hair loss and a scaly, erythematous dermatitis around body orifices. (D.M. Mock, et al, Semin Dermatol 1991 Dec;10(4):296-302)

Studies in animals show vitamins such as biotin are essential in the metabolism of the keratinizing epidermal cells and therefore form part of the link between nutrition and hoof [nail] quality. (C.K. Mulling, et al, Anat Histol Embryol 1999 May;28(2):103-8)

A study on ponies found that animals supplemented with biotin for five months had a 15% greater growth rate for hoofs and hoof than control animals. (J.D. Reilly, et al, Equine Vet J Suppl 1998 Sep;(26):51-7)

A study of 108 horses with brittle hoof horn or chipped hooves over 1 to 6 years, found that horses supplemented with 5 mg biotin per 100 to 150 kg body weight, per os, daily, improved the condition of their hooves after 8 to 15 months supplementation. The improvement was not seen in controls. (H. Geyer, et al, Schweiz Arch Tierheilkd 1994;136(4):137-49)

Microscopic observations of claw horns of pigs supplemented with biotin showed that there was an increase in the density of horn tubules and that they were more clearly defined, horny squames were more tightly packed, and there were alterations in the structure of the coronary skin. (S.A. Kempson, et al, Vet Rec 1989 Jan 14;124(2):37-40)

Molecular studies show that biotin directly stimulates the differentiation of epidermal cells. Biotin definciency in animals also causes pathological changes of the skin and its appendages including excessive peeling and dryness (exfoliative dermatitis), depigmentation, and hair loss. The hooves of biotoin deficient swine are weak and brittle. Biotin supplementation noticeably improves hoof quality of horses, cattle and swine even when there is no apparent biotin deficiency. (A. Friysche, et al, Schweiz Arch Tierheilkd 1991;133(6):277-83)

Addition of biotin to cells cultured in a biotin deficient medium results in enhanced protein synthesis, DNA synthesis and cell growth. (R.P. Bhullar, et al, J Cell Physiol 1985 Jun;123(3):425-30)

Pantothenic Acid

Pantothenic acid, also called vitamin B5, is a water-soluble vitamin involved in the Kreb's cycle of energy production and is needed to make the neurotransmitter acetylcholine. It is also essential in producing, transporting, and releasing energy from fats. Synthesis of cholesterol (needed to manufacture vitamin D and steroid hormones) depends on pantothenic acid. Pantothenic acid also activates the adrenal glands. (Fidanza A. Therapeutic action of pantothenic acid. *Int J Vitam Nutr Res* 1983;suppl 24:53–67).

In a prospective, double-blind randomized study of 49 patients undergoing surgery for tattoos, of whom 18 were supplemented with 1 g ascorbic acid and 0.2 g pantothenic acid daily for 21 days, results suggested supplementation may benefit wound healing through variations in trace element content of skin and scars. Trace elements are correlated to mechanical properties of scars. (F. Vaxman, et al, Eur Surg Res 1995;27(3):158-66)

A study in animals found that supplementation with pantothenic acid induced an accelerated effect of the normal healing process. The mechanism responsible for this improvement seemed to be an increase in cellular multiplication. (M. Aprahamian, et al, Am J Clin Nutr 1985 Mar;41(3):578-89)

Magnesium

Data from the CARDIA study, involving 2643 black and 2472 white men and women aged 18-30 years found that insulin was positively correlated with serum glucose and negatively correlated with magnesium intake. (T.A. Manolio, et al, J Clin Epidemiol 1991;44(6):571-8)

Rats fed a magnesium deficient diet have a lower endurance capacity than rats fed a control diet. This result is probably due to multiple factors affected by dietary magnesium intake, including changes in insulin levels, calcium concentrations in plasma and gastrocnemius muscle, trace element concentrations in tissue, and alterations in body composition. (P. Lowney, et al, Biol Trace Elem Res 1988 Jun;16(1):1-18)

In young, apparently healthy trained Israeli men, strenuous effort gave rise to persistent magnesium deficiency. (G. Stendig-Lindberg, J Basic Clin Physiol Pharmacol 1992 Apr Jun;3(2):139-51)

The central nervous system concentration of magnesium appears to have a critical level below which neurologic dysfunction occurs. (W.F. Langley, et al, Arch Intern Med 1991 Mar; 151 (3): 593-6)

Iron

Short-term moderate iron deficiency was accompanied by decreased platelet concentrations, increased activity of serum enzymes indicative of cell damage, and increased liver copper concentrations in rats. (G.l. Stangl, et al, Z Ernahrungswiss 1998 Sep;37(3):260-8)

Iron deficiency selectively affects the integrity of the blood-brain barrier for insulin, glucose, and valine transport. (D. Ben-Shachar, et al, J Neurochem 1988 May; 50(5):1434-7)

Iron is an integral part of many proteins and enzymes that maintain good health. In humans, iron is an essential component of proteins involved in oxygen transport. (Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Washington, DC: National Academy Press, 2001. Dallman PR. Biochemical basis for the manifestations of iron deficiency. Annu Rev Nutr 1986;6:13-40.)

A deficiency of iron limits oxygen delivery to cells, resulting in fatigue, poor work performance, and decreased immunity. (Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:691S-6S. Bhaskaram P. Immunobiology of mild micronutrient deficiencies. Br J Nutr 2001;85:S75-80.)

Zinc

Zinc is necessary in the regulation of male hormones (testosterone) and is an important mineral in prostate gland function and sperm production. Zinc deficiency can lead to a depletion of testosterone and inhibition of spermatozoa production. Zinc is also thought to help extend the functional life span of the ejaculated spermatozoa. In a study of 53 infertile men, zinc was positively correlated with the concentration of moving sperm in the group of middling sperm motility. H. Ota, Jap Journal Fertility & Sterility 1995;40/1:78-82

Zinc and folic acid may help increase sperm count. In a double-blind randomised placebo-controlled trial, of 108 fertile and 103 sub-fertile men, taking zinc and folic acid supplements, the total normal sperm count increased after combined zinc sulphate and folic acid treatment in both the sub-fertile and fertile men. Results were significantly high in the sub-fertile group, demonstrating a 74% increase in total normal sperm count. (Wai Yee Wong et al, Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial, Fertility and Sterility, March 2002, Vol 77, Issue 3, Pages 491-498)

A daily intake of zinc is required to maintain a steady state because the body has no specialized zinc storage system. (Rink L, Gabriel P. Zinc and the immune system. Proc Nutr Soc 2000;59:541-52. [PubMed abstract])

Zinc deficiency is characterized by growth retardation, loss of appetite, and impaired immune function. In more severe cases, zinc deficiency causes hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and eye and skin lesions. (Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, 2001.)

A 26-week, double-blind, placebo-controlled trial compared the effects of treatment with zinc (66 mg of zinc sulfate, supplying 15 mg of zinc), folate (5 mg), and zinc plus folate against placebo.[22] A total of 108 fertile men and 103 men with impaired fertility ("subfertile men") participated in the study. The two supplements combined significantly improved the sperm count and the percentage of healthy sperm in the subfertile men. (Wong WY, Merkus HM, Thomas CM, et al. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. *Fertil Steril.* 2002;77:491-498.)

Zinc deficiency leads to reduced numbers of sperm and impotence in men. (Prasad AS, Cossack ZT. Zinc supplementation and growth in sickle cell disease. *Ann Intern Med* 1984;100:367–71.)

The correlation between blood levels of zinc and sperm quality remains controversial. Infertile men have been reported to have lower levels of zinc in their semen, than do men with normal fertility. (Kvist U, Kjellberg S, Bjorndahl L, et al. Seminal fluid from men with agenesis of the Wolffian ducts: zinc-binding properties and effects on sperm chromatin stability. *Int J Androl* 1990;13:245–52.)

Men with normal sperm density tend to have higher amounts of zinc in their semen, than do men with low sperm counts. (Saaranen M, Suistomaa U, Kantola M, et al. Lead, magnesium, selenium and zinc in human seminal fluid: comparison with semen parameters and fertility. *Hum Reprod* 1987;2:475–9.)

A few studies have shown that oral zinc supplementation improves both sperm count motility, and the physical characteristics of sperm in some groups of infertile men. (Stankovic H, Mikac-Devic D. Zinc and copper in human semen. *Clin Chim Acta* 1976;70:123–6. Hartoma TR, Nahoul K, Netter A. Zinc, plasma androgens and male sterility. *Lancet* 1977;2:1125–6. Stankovic H, Mikac-Devic D. Zinc and copper in human semen. *Clin Chim Acta* 1976;70:123–6. Kynaston HG, Lewis-Jones DI, Lynch RV, Desmond AD. Changes in seminal quality following oral zinc therapy. *Andrologia* 1988;20:21–2.)

For infertile men with low semen zinc levels, a preliminary trial found that zinc supplements (240 mg per day) increased sperm counts and possibly contributed to successful impregnation by 3 of the 11 men. (Marmar JL, Katz S, Praiss DE, DeBenedictis TJ. Semen zinc levels in infertile and postvasectomy patients and patients with prostatitis. *Fertil Steril* 1975:26:1057–63.)

In a controlled trial, 100 men with low sperm motility received either 57 mg of zinc twice daily or a placebo. After three months, there was significant improvement in sperm quality, sperm count, sperm motility, and fertilizing capacity of the sperm. (Omu AE, Dashti H, Al-Othman S. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. *Eur J Obstet Gynecol Reprod Biol* 1998;79:179–84.)

Copper

Copper - the activity of copper and zinc containing superoxide dismutase is higher in seminal plasma with spermatozoa of good motility than low motility. In a study of 18 fertile and 172 infertile men, sperm concentration, percentage progressive motility and normal morphology were significantly correlated with copper concentrations in semen. (F. Jockenhovel, et al, Andrologia 1990 Nov-Dec;22(6):503-11)

In a study of 41 trained male athletes and 24 controls, runners had lower serum copper concentrations than controls. (A. Resina, et al, Int J Sports Med 1990 Feb;11 (1):58-60)

Copper-zinc superoxide dismutase is believed to play a major role in the first line of antioxidant defense. (Y.S. Ho, et al, J Biol Chem 1998 Mar 27;273(13):7765-9)

Men and women fed diets close to 1 mg of copper per day, amounts quite frequent in the US, responded similarly to deficient animals with reversible, potentially harmful changes in blood pressure control, cholesterol and glucose metabolism and electrocardiograms. (L.M. Klevay, J Am Coll Nutr 1998 aug;17(4):322-6)

Copper is an essential trace metal which plays a fundamental role in the biochemistry of the human nervous system. Recent studies have also implicated copper in the pathogenesis of neuronal injury in Alzheimer's disease. (D.J. Waggoner, et al, Neurobiol Dis 1999 Aug;6(4):221-30)

Activity of the antioxidant enzyme superoxide dismutase was significantly reduced in the livers of rats consuming a copper deficient diet. (S.I. Dashti, et al, Nutrition 1995 Sep-Oct;11(5 Suppl):564-7)

Manganese

High physical exertion produced an increased excretion of iron, copper, manganese, and zinc from qualified skiers. Results suggest that the diet of athletes be enriched with trace elements, especially with iron in the course of rehabilitation after intensive training and competitions. (V.I.a Rusin, et al, Vopr Pitan 1980 Jul-Aug; (4):15-9)

Administration of therpeutic doses of iron raises copper and manganese excretion from the body. (V. V. Nasolodin, et al, Ter Arkh 1984; 56(9): 116-9)

The optic nerve needs manganese for the maintenance of its cell structure. (H. Gong, et al, Exp Eye Res 1999 Mar; 68(3):313-20)

Biotic doses of trace elements iron, copper, and manganese exert a favourable effect on working capacity of athletes. (K.L. Vlasenko, et al, Vopr Pitan 1980 Jul-Aug; (4): 9-22)

Selenium

Selenium appears to be essential for normal spermatozoa development. In a study of semen samples from 184 men attending a clinic for fertility investigation, a significant positive correlation was obtained between seminal plasma selenium concentrations and concentrations of spermatozoa in ejaculate. (N.B. Oldereid, et al, Hum Reprod 1998 Aug;13(8):2172-6)

Another study to determine whether the decline in selenium intake and status in men in the West of Scotland might be a contributory factor to male sub-fertility had the same outcome – that selenium supplementation can improve sperm motility and the chance of successful conception. (Scott R et al, The effect of oral selenium supplementation on human sperm motility Br J Urol, 1998 Jul;82(1):76-80)

In a double-blind study of infertile men with reduced sperm motility, supplementation with selenium (100 mcg per day for three months) significantly increased sperm motility, but had no effect on sperm count. Eleven percent of 46 men receiving selenium achieved paternity, compared with none of 18 men receiving a placebo. (Scott R, MacPherson A, Yates RWS, et al. The effect of oral selenium supplementation on human sperm motility. *Br J Urol* 1998;82:76–80.)

Currently, biomedical research is showing interest in the anti-oxidant activity of selenium. This could be due to compelling evidence that reported that oxidative damage to cells and cell membranes is one of the causative agents in the pathogenesis of many disease states including male infertility. Selenium is a trace element which may be found in soil, water and some foods and is considered to be an essential element which plays an active role in several metabolic pathways and is believed to perform several important roles in the human body. These roles include anti-oxidative activities at cellular level and participating in different enzyme systems. Selenium also serves as a vital component in the maintenance of muscle cell and red blood cell integrity, playing a role in the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It has also been reported that selenium is essential in the detoxification of toxic metals in the human system, foetal respiration and energy transfer reactions as well as in the production of sperm cells. It is thought that male infertility can be the result of a selenium deficiency as the absence of selenium in the testicular tissues induces degeneration which results in the active impairment of sperm motility as the first indication of impending infertility. (Selenium: its potential role in male infertility, Pak J Med Sci April - June 2009 Vol. 25 No. 2 332-337)

Selenium is needed for immune, thyroid, and liver function. It also acts as an antioxidant and may prevent the formation of certain cancers, like that of the prostate. (Clark LC et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 1998;81:730-734.)

Chromium

Chromium has become a popular supplement for carbohydrate metabolism, and for good reason. Chromium is part of the glucose tolerance factor. It has been shown to reduce blood glucose, hemoglobin A1c levels, and serum cholesterol. (Evans GW et al. Cholesterol and glucose lowering effect of chromium picolinate. FASEB 1989;3:A761.)

Chromium is an essential nutrient involved in the regulation of carbohydrate and lipid metabolism. Normal dietary intake of chromium in humans and farm animals is often suboptimal. In addition to its effects on glucose, insulin, and lipid metabolism, chromium has been reported to increase lean body mass and decrease percentage body fat, which may lead to weight loss in humans. These effects are supported by animal studies. There have been no confirmed negative effects of chromium in nutritional studies. (R.A. Anderson, et al, Nutr Rev 1998 Sep;56(9):266-70)

It is estimated that most individuals are not ingesting sufficient amounts of chromium in their diets. Chromium deficiency is thought to contribute to glucose intolerance and unhealthy blood lipid profiles. The primary function of chromium is to potentiate the effects of insulin, and thereby alter glucose, amino acid and fat metabolism. (P.M. Clarkson, et al, Sports Med 1997 Jun;23(6):341-9)

Most diets contain less than 60% of the minimum suggested intake of 50 mcg chromium. Insufficient dietary intake of chromium leads to signs and symptoms similar to those observed for diabetes and cardiovascular disease. Trivalent chromium has a very large safety range and there have been no documented signs of chromium toxicity in any of the nutritional studies at levels up to 1 mg per day. (R.A. Anderson, Regul Toxicol Pharmacol 1997 Aug;26(1 Pt 2):S35-41)