



Fertility problems

Indications

Infertility is a global issue affecting both men and women almost equally (1). In the UK around 1 in 7 couples are estimated to have fertility problems (2).

Investigation via the NHS is available only after one or more years (or 6 months in women over 35) of unprotected sex.

Investigations may include semen analysis, assessment of ovulation, tubal damage and uterine abnormalities as well as screening for Chlamydia trachomatis and susceptibility to rubella (2). The following tests may be offered; Follicle Stimulating Hormone (FSH), Oestradiol, Luteinising Hormone (LH), Progesterone, Testosterone, Prolactin. Ultrasound and X-ray may also be offered.

Statistics from NICE reveal that the causes of infertility fall into the following categories (% figure is an estimate) (2);

- Ovulatory disorders (25%)
- Tubal damage (20%)
- Male infertility (30%) (low sperm counts, poor sperm quality and poor sperm motility, hormone imbalance) (3)
- Uterine or peritoneal disorders (10%)

Following NHS investigations approximately 25% of men and women present with 'unexplained fertility' (2).

Tests available from the NHS firstly are only available after one or more years and focus mainly on hormone levels and sperm quality. From a functional perspective, considering the interconnected nature of the human body, there may be many other factors that affect fertility in men and women, additional nutritional and functional testing therefore may be applicable and prove beneficial in the following areas;

Screening

Nutritional status, environmental exposures and functional issues may affect the ability to conceive as well as the health of the foetus and factors such as birth weight (4,5,6). Nutritional and functional testing pre conceptually may therefore be beneficial for any couple planning a pregnancy. The EpiGen Global Research Consortium are set to run a trial in Southampton, Singapore and New Zealand named 'Nutritional Intervention Preconception and during Pregnancy to maintain healthy glucose levels and offspring health (NiPPeR)'. Results from this study will be very interesting and may give further support to the recommendation.

Diagnosis and Post diagnosis

Nutritional and functional testing may be beneficial in addition to mainstream testing methods (outlined above) for diagnosis and post diagnosis and may be supportive to intervention decisions, for example IVF (7). These tests may also prove beneficial for the 25% of cases that have 'unexplained infertility' (8,9).

Recommended Tests

Vitamin profile plus Vitamin D, B12 and folate

Intake of micronutrients have been linked with enhanced fertility and it has been documented that users of micronutrient supplements had increased pregnancy rates. Folate status seems particularly important via its role in the ovarian response to FSH. B vitamins are also positively associated with fertility (10) and may help protect against the negative reproductive effects of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) exposure (11).

Vitamin D receptors are expressed in both male and female reproductive tissue. Adequate serum Vitamin D levels are associated with intracellular calcium concentrations and sperm motility and function (12) and studies support the suggestion that fertility may be impaired in women with low Vitamin D levels (13).

Vitamins such as Vitamin E and C, and carotenoids have also been shown to have antioxidants benefits, as discussed below in the mineral profile section (14,15).

[Sample requirements: clotted blood tube (gold top) for fat soluble vitamins & B12, heparin (green top) for B vitamins and EDTA (lavender top) for folate]

Plasma mineral profile with red cell magnesium

Antioxidant minerals such as zinc, copper and selenium have been shown to have a positive effect on sperm quality and pregnancy rate (14,16,17). Zinc is essential for normal growth, development and reproduction. Spermatogenesis, sperm motility and DNA integrity is also dependant on zinc (18). Zinc is also essential for female reproduction, including embryogenesis and development (18).

[Sample requirement: Trace element free plasma (navy blue top tube), heparin [green top] and clotted blood tube (gold top)]

Urine iodine

See Thyroid profile (29,30). Iodine requirements increase by over 50% during pregnancy (31). Deficiency during pregnancy can cause hypothyroidism and impair neurological development of the foetus and may manifest as cretinism (31).

[Sample requirement: random, mid-stream, urine specimen]

Fatty acids - Erythrocytes

Essential fatty acids (EFA's) are important components of cell membranes, including that of sperm. EFA's play a vital role in sperm function and the ability of sperm to fertilise an egg. On the contrary, trans fatty acid intake is associated with low sperm concentrations and is inversely related to total sperm count in men. Saturated fat intake is also associated negatively with sperm concentration (3). Omega 3 is essential for cholesterol synthesis, the precursor for oestradiol, and therefore EFA intake has been associated with an increased number of follicles, improved embryo morphology and improvements in ovulation (19).

Trans fatty acids are also known to bind to peroxisome proliferator activated receptor γ (PPAR- γ), which play a vital role in placental maturation, function and hormone secretion, and have been associated with pregnancy loss (20,21). Omega 3 fatty acids are vital during pregnancy as building blocks of the foetal brain and retina (22).

[Sample requirement: EDTA (lavender top)]

MTHFR (Homocysteinaemia) - saliva genetic screen

The Methylene tetrahydrofolate reductase (MTHFR) A1298C polymorphism is thought to affect a high percentage of Europeans. Folate and homocysteine are important for maintaining pregnancy. Folate is required for DNA synthesis and cell division and is metabolised through the one carbon metabolism pathway. MTHFR A1298C polymorphism affects folate metabolism via this pathway and results in hyperhomocysteinemia. Hyperhomocysteinemia is thought to be a risk factor for neural tube defects and placental abruption. The MTHFR polymorphism is thought to be linked with pregnancy loss (23,24).

[* Saliva sample, kit available on request]

Toxic metals

Exposure to environmental and occupational metals such as lead and cadmium may lead to accumulation in male reproductive organs. This accumulation may have effects on hormone concentrations, fertility and sperm parameters (25). Heavy metals such as arsenic, lead copper and mercury effect reproductive health and may be toxic to the developing foetus (26).

[Sample requirement: Trace element free plasma (navy blue top tube)]

Toxic organic chemical exposure profile

Phthalates are found in abundance in the environment; from flooring to food packaging and so human exposure is widespread and usually occurs via ingestion. There is evidence to support a link with phthalates and reproductive disruption (27)

[* Sample requirement: Mid-stream, early morning, urine specimen]

Thyroid profile

The thyroid gland controls rate of metabolic processes and is under the control of the hypothalamus and pituitary gland (HPT axis). Hyperthyroidism and hypothyroidism have been shown to affect the release of gonadotrophin-releasing hormone which is required for FSH and LH and ovulation. Women with sub fertility appear to have raised serum TSH levels. Autoimmune conditions such as antiphospholipids antibodies, diabetes mellitus and systemic lupus erythematosus have also been implicated in sub fertility (29,30).

[Sample requirement: clotted blood tube (gold top)]

Adrenal stress profile

The hypothalamus-pituitary-adrenal axis (HPA axis) is directly affected in times of stress and responds via increased levels of glucocorticoids. The glucocorticoids promote gluconeogenesis, mobilise amino acids, and stimulate fat breakdown. Elevated levels of glucocorticoids are known to inhibit reproduction and may therefore effect fertility (28).

[* Saliva sample, kit available on request]

Coeliac/gluten screen

Coeliac disease is an autoimmune disorder triggered by ingestion of gluten. Poor nutrient absorption is often associated with coeliac disease, with particular concern over B vitamin status. Maternal coeliac disease may be associated with recurrent foetal loss, growth restrictions, preterm delivery and low birth weight (32,33).

[Sample requirement: clotted blood tube (gold top)]

Glutathione peroxidase

Oxidative stress results in an increase in reactive oxygen species (ROS) which cause a pathological reaction which damage sperm cells and results in a decrease in sperm numbers, reduced motility and impairs function. Glutathione, along with dietary antioxidants such as Vitamin E and C, zinc and selenium may be supportive to reduce damage from ROS (16).

[Sample requirement: heparin blood (green top tube)]

Superoxide dismutase

Superoxide dismutase (SOD), an enzyme that catalyses the dismutation of the superoxide radical into oxygen or hydrogen peroxide. SOD, along with its antioxidant benefits is thought to be an important component of implantation (17).

[Sample requirement: heparin blood (green top tube)]

Patient preparation

Patients should avoid mineral and vitamin supplements for 24-48 hours prior to providing blood & urine samples for above tests and should follow any other individual test instructions provided with test kits.

Turn around time

Typically 3-5 working days for tests performed at Biolab, but up to 15 working days for samples referred to laboratories outside of the UK (*)

Prepared by Hayley Jones on behalf of Biolab (Nov 2015)

References

1. Mascarenhas, M.N. et al., 2012. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS medicine*, 9(12), p.e1001356. Available at: <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001356> [Accessed September 30, 2015].
2. Anon, Fertility | Introduction | Guidance and guidelines | NICE. Available at: <https://www.nice.org.uk/guidance/cg156/chapter/Introduction> [Accessed October 15, 2015].
3. Eslamian, G. et al., 2015. Dietary fatty acid intakes and asthenozoospermia: a case-control study. *Fertility and sterility*, 103(1), pp.190–8. Available at: <http://www.fertstert.org/article/S0015028214022602/fulltext> [Accessed October 12, 2015].
4. Hambidge, K. et al., 2014. Preconception maternal nutrition: a multi-site randomized controlled trial. *BMC Pregnancy and Childbirth*, 14(1), p.111. Available at: <http://www.biomedcentral.com/1471-2393/14/111> [Accessed October 19, 2015].
5. Allen, L.H., 2005. Multiple micronutrients in pregnancy and lactation: an overview. *Am J Clin Nutr*, 81(5), p.1206S–1212. Available at: <http://ajcn.nutrition.org/content/81/5/1206S.full> [Accessed October 19, 2015].
6. Grieger, J.A., Grzeskowiak, L.E. & Clifton, V.L., 2014. Preconception dietary patterns in human pregnancies are associated with preterm delivery. *The Journal of nutrition*, 144(7), pp.1075–80. Available at: <http://jn.nutrition.org/content/144/7/1075.full> [Accessed October 19, 2015].
7. Vujkovic, M. et al., 2010. The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. *Fertility and sterility*, 94(6), pp.2096–101. Available at: <http://www.fertstert.org/article/S0015028209043386/fulltext> [Accessed October 19, 2015].
8. Quaas, A. & Dokras, A., 2008. Diagnosis and treatment of unexplained infertility. *Reviews in obstetrics & gynecology*, 1(2), pp.69–76. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2505167&tool=pmcentrez&rendertype=abstract> [Accessed August 16, 2015].
9. Ruder, E.H. et al., 2014. Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. *Fertility and Sterility*, 101(3), pp.759–766. Available at: <http://www.fertstert.org/article/S0015028213032615/fulltext> [Accessed October 19, 2015].
10. Chavarro, J.E. et al., 2008. Use of multivitamins, intake of B vitamins, and risk of ovulatory infertility. *Fertility and sterility*, 89(3), pp.668–76. Available at: <http://www.fertstert.org/article/S001502820700828X/fulltext> [Accessed September 12, 2015].
11. Ouyang, F. et al., 2014. Preconception serum 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane and B-vitamin status: independent and joint effects on women's reproductive outcomes. *American Journal of Clinical Nutrition*, 100(6), pp.1470–1478. Available at: <http://ajcn.nutrition.org/content/100/6/1470.abstract> [Accessed October 12, 2015].
12. Blomberg Jensen, M. et al., 2011. Vitamin D is positively associated with sperm motility and increases intracellular calcium in human spermatozoa. *Human reproduction (Oxford, England)*, 26(6), pp.1307–17. Available at: <http://humrep.oxfordjournals.org/content/26/6/1307.abstract> [Accessed October 12, 2015].
13. Lerchbaum, E. & Obermayer-Pietsch, B., 2012. Vitamin D and fertility: a systematic review. *European journal of endocrinology / European Federation of Endocrine Societies*, 166(5), pp.765–78. Available at: <http://www.eje-online.org/content/166/5/765.abstract> [Accessed October 12, 2015].
14. Ross, C. et al., 2010. A systematic review of the effect of oral antioxidants on male infertility. *Reproductive biomedicine online*, 20(6), pp.711–23. Available at: <http://www.rbmojournal.com/article/S1472648310001331/fulltext> [Accessed October 12, 2015].
15. Zareba, P. et al., 2013. Semen quality in relation to antioxidant intake in a healthy male population. *Fertility and Sterility*, 100(6), pp.1572–1579. Available at: <http://www.fertstert.org/article/S0015028213029981/fulltext> [Accessed October 12, 2015].
16. Walczak-Jedrzejowska, R., Wolski, J.K. & Slowikowska-Hilczler, J., 2013. The role of oxidative stress and antioxidants in male fertility. *Central European Journal of Urology*, 65(1), pp.60–67. Available at: <http://europepmc.org/articles/PMC3921845/?report=abstract> [Accessed October 2, 2015].

17. Ruder, E.H. et al., 2008. Oxidative stress and antioxidants: exposure and impact on female fertility. *Human reproduction update*, 14(4), pp.345–57. Available at: <http://humupd.oxfordjournals.org/content/14/4/345.abstract> [Accessed August 29, 2015].
18. Murarka, S. et al., 2015. Role of Zinc in Reproductive Biology - An Overview. *Austin J Reprod Med Infertil*. 2015;2(2): 1009.
19. Hammiche, F. et al., 2011. Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. *Fertility and Sterility*, 95(5), pp.1820–1823. Available at: <http://www.fertstert.org/article/S0015028210028074/fulltext> [Accessed October 12, 2015].
20. Morrison, J.A., Glueck, C.J. & Wang, P., 2008. Dietary trans fatty acid intake is associated with increased fetal loss. *Fertility and Sterility*, 90(2), pp.385–390. Available at: <http://www.fertstert.org/article/S0015028207013805/fulltext> [Accessed October 12, 2015].
21. Chavarro, J.E. et al., 2007. Dietary fatty acid intakes and the risk of ovulatory infertility. *The American journal of clinical nutrition*, 85(1), pp.231–7. Available at: <http://ajcn.nutrition.org/content/85/1/231.abstract> [Accessed October 12, 2015].
22. Coletta, J.M., Bell, S.J. & Roman, A.S., 2010. Omega-3 Fatty acids and pregnancy. *Reviews in obstetrics & gynecology*, 3(4), pp.163–71. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3046737&tool=pmcentrez&rendertype=abstract> [Accessed October 29, 2015].
23. Nair, R.R. et al., 2013. Association of maternal and fetal MTHFR A1298C polymorphism with the risk of pregnancy loss: a study of an Indian population and a meta-analysis. *Fertility and sterility*, 99(5), pp.1311–1318.e4. Available at: <http://www.fertstert.org/article/S0015028212025368/fulltext> [Accessed October 13, 2015].
24. Rosen, M.P. et al., 2007. Methylenetetrahydrofolate reductase (MTHFR) is associated with ovarian follicular activity. *Fertility and Sterility*, 88(3), pp.632–638. Available at: <http://www.fertstert.org/article/S0015028206047224/fulltext> [Accessed October 13, 2015].
25. Benoff, S., 2000. Male infertility and environmental exposure to lead and cadmium. *Human Reproduction Update*, 6(2), pp.107–121. Available at: <http://humupd.oxfordjournals.org/content/6/2/107.abstract> [Accessed October 12, 2015].
26. Neeti, K. and Prakash, T., 2013. Effects of Heavy Metal Poisoning during Pregnancy. *Int. Res. J. Environment Sci*. 2(1), pp. 88-92.
27. Dodge, L. et al., 2015. Associations between paternal urinary phthalate metabolite concentrations and reproductive outcomes among couples seeking fertility treatment. *Reproductive Toxicology*. Available at: <http://www.sciencedirect.com/science/article/pii/S0890623815300253>.
28. Whirledge, S. & Cidlowski, J.A., 2010. Glucocorticoids, stress, and fertility. *Minerva endocrinologica*, 35(2), pp.109–25. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3547681&tool=pmcentrez&rendertype=abstract> [Accessed September 29, 2015].
29. Krassas, G.E., 2000. Thyroid disease and female reproduction. *Fertility and Sterility*, 74(6), pp.1063–1070. Available at: <http://www.fertstert.org/article/S0015028200015892/fulltext> [Accessed October 12, 2015].
30. Jefferys, A., Vanderpump, M. & Yasmin, E., 2015. Thyroid dysfunction and reproductive health. *The Obstetrician & Gynaecologist*, 17(1), pp.39–45. Available at: <http://doi.wiley.com/10.1111/tog.12161> [Accessed October 12, 2015].
31. Zimmermann, M.B., 2012. The effects of iodine deficiency in pregnancy and infancy. *Paediatric and perinatal epidemiology*, 26 Suppl 1, pp.108–17. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22742605> [Accessed July 14, 2015].
32. Meloni, G.F. et al., 1999. The prevalence of coeliac disease in infertility. *Human Reproduction*, 14(11), pp.2759–2761. Available at: <http://humrep.oxfordjournals.org/content/14/11/2759.abstract> [Accessed October 12, 2015].
33. Choi, J.M. et al., Increased prevalence of celiac disease in patients with unexplained infertility in the United States. *The Journal of reproductive medicine*, 56(5-6), pp.199–203. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3122153&tool=pmcentrez&rendertype=abstract> [Accessed August 21, 2015].

Advisory note:

This guide to a disease specific recommended panel of tests, lists those nutritional & biochemical pathology investigations that are justified in current medical literature and which may be appropriate for some individuals. These are guidelines only and individual requirements will vary depending on multiple factors (diet, use of nutritional supplements, food exclusions etc).