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Information for couples with Recurrent Pregnancy Loss

Patient leaflet based on the ESHRE Guideline on Recurrent Pregnancy Loss

Version 2017

Introduction

This booklet is for you if:

- You have experienced at least 2 pregnancy losses
- You have been diagnosed with Recurrent Pregnancy Loss

This booklet is intended for patients, but may also be useful for their family members and caregivers.

This booklet aims to:

- increase awareness of Recurrent Pregnancy Loss (or RPL) .
- provide couples with information on appropriate tests and treatments.
- provide couples with tools to discuss their options with their healthcare provider.

Content:

This booklet and the information presented are entirely-based on the ESHRE Guideline on Recurrent Pregnancy Loss. All the information and recommendations in the guideline are built upon the best available evidence from research. Where there is insufficient evidence from research, a group of experts has formulated recommendations based on their clinical expertise. The experts also formulated areas of research to improve future clinical care for couples with Recurrent Pregnancy Loss.

We have added the following symbols to explain the strength of the recommendations

	Strong recommendation based on research evidence
	Recommendation based on considered opinion of the guideline development group

More information is available in the last pages of this booklet, including a list of medical and research terms and their meanings. The full guideline is available on the website of ESHRE (www.eshre.eu/guidelines)

What is Recurrent Pregnancy Loss?

A **pregnancy loss** is the spontaneous loss of a pregnancy before 24 weeks of gestation[1]. The loss of a pregnancy after 24 weeks' gestation is called a stillbirth, and is not discussed in this leaflet.

A diagnosis of Recurrent Pregnancy Loss or **RPL** could be considered after the loss of two or more pregnancies. This includes pregnancies after spontaneous conception and after assisted reproduction (e.g. IUI and IVF/ICSI). Ectopic pregnancies and molar pregnancies are not included.

RPL is also sometimes called recurrent miscarriage, although this term should be reserved for **cases where all pregnancy losses have been confirmed as intrauterine miscarriages.**

Primary RPL is a term used for women who have not had a baby before their pregnancy losses. **Secondary RPL** means they have had at least one baby before their losses. **Consecutive pregnancy losses** are losses that happen one after the other, without a baby in between losses.

It is estimated that up to 15% of pregnancies result in pregnancy loss. RPL affects 1 to 2% of couples.

Emotional impact

A single pregnancy loss can have a significant emotional impact on women and their partners, and this impact may increase with each additional loss. You may experience feelings of loss, grief or a sense of failure; this is normal and understandable.

Your partner may feel or react differently from you.

It may help to talk to your doctor about your feelings. Your doctor may suggest a referral for professional support, if (s)he believes this could help. You can also seek support from patient organisations (see further details on page 14).

[1] This is the definition used by the guideline group. The cut-off point may be lower or higher in some countries.

Which tests should my doctor perform?

Several investigations have been suggested for couples with RPL. The aim of doing such tests could be to:

- identify the cause, or likely cause, of the previous pregnancy loss(es)
- recommend or suggest appropriate treatment, if that is an option
- help the doctor to estimate your prognosis (the chance of having a baby in the future)

Only a few of the suggested tests for couples with RPL have been found to be useful, and are therefore recommended for all couples with RPL.

> Even if a cause is found, there may not be a treatment.

For example, you may have antibodies which are believed to be a contributing factor in RPL, but there are currently no treatments available to increase your chances of a successfull pregnancy.

> In the majority of RPL couples, no cause is found. This is called unexplained RPL.

In the next section, we discuss investigations that are **recommended** for all couples with RPL, and tests that **might be considered** for some couples depending on their medical and family history.

Investigations that are recommended:

Assessment of your medical and family history.

If you (or your family members) have been diagnosed in the past with one of the following medical conditions, it is important to inform your doctor:

- Congenital abnormalities (Heart defect, Spina Bifida, Down's Syndrome, other syndromes)
- Thrombophilia, Thromboembolism (blood clotting problems, stroke)
- Polycystic ovary syndrome (PCOS)
- Diabetes or Thyroid abnormalities
- No periods or irregular periods (Amenorrhea or Oligomenorrhea)

Screening for antiphospholipid syndrome (APS)

When you cut your finger, the blood will clot to stop you losing too much blood. Thrombophilia is a condition that makes the blood clot more than it should. Thrombophilia can be **inherited** (passed down genetically) or it can be **acquired** (not inherited). When it is acquired, and there is also a history of pregnancy loss, it is called **antiphospholipid syndrome** or APS.

Testing for antiphospholipid syndrome (APS) is done by a blood test for lupus anticoagulant, and anticardiolipin and maybe also aβ2GPI antibodies. The results can provide information to:

(1) make a diagnosis of APS,

(2) show a contributing factor of the pregnancy losses,

(3) recommend possible treatment for APS and RPL, and

(4) help to prevent other pregnancy complications associated with APS (for instance pre-eclampsia).

It is unclear whether inherited thrombophilia could also be a cause of RPL.

Screening for thyroid dysfunction

The thyroid gland produces several hormones involved in many processes in the body. When there are problems in the way the thyroid gland functions, this can lead to over-production or under-production of thyroid hormones.

Under-production of thyroid hormones (hypothyroidism) is often found in women with RPL, and may increase the risk for pregnancy loss. Over-production of thyroid hormones (hyperthyroidism) is associated with several pregnancy complications, although not with pregnancy loss.

Thyroid antibodies, called TPO antibodies, could lead to thyroid dysfunction. TPO antibodies are associated with RPL. The results of screening can provide information to

(1) make a diagnosis of thyroid dysfunction,

(2) show a possible cause or contributing factor for the pregnancy losses,

(3) recommend possible treatment.

Pelvic examination (usually ultrasound)

If there is a problem with the shape of the uterus (womb), a fetus may not be able to develop and this increases the chance of a pregnancy loss.

Your doctor should perform an ultrasound scan to check the shape of your uterus and to examine it for any malformations or abnormalities. Your doctor may use other techniques or equipment to screen, or to confirm the ultrasound results.

Additional investigations that could be considered based on medical and family history:

Genetic analysis 

The genes of a person are like a book full of recipes. There is a gene combination for the colour of the eyes, the shape of the nose, and so on. The genes of a fetus are a combination of the genes of the mother and of the father. When the genes are combined during conception (when egg and sperm meet), errors can occur. Some of these errors or abnormalities can be significant and result in a fetus that cannot survive. As such, genetic errors in the fetus could be the cause of a pregnancy loss, and are more frequent in older women.

Genetic testing on pregnancy tissue (called **fetal karyotyping**) is not recommended in all cases of RPL, but your doctor might consider it to try to identify the cause of any particular loss. If the testing shows that there was a genetic error or abnormality in the fetus, this means that it might be the cause of this pregnancy loss. This may be important information for you, even though it doesn't tell you if your other loss/es happened for the same reason. It is also important to know that there are no treatments to improve the chances of a healthy baby in the next pregnancy.

Genetic testing on both parents (called **parental karyotyping**) can show a genetic abnormality that does not cause a problem in the parent, but may cause a genetic defect in the fetus. The chances of finding a genetic abnormality in the parents is small, and even if an abnormality is found, the chances of a healthy baby are still good.

If you have a family member with a congenital abnormality (Heart defect, Spina Bifida, Down's Syndrome, or other syndromes), you may have a higher chance of carrying a genetic abnormality, and your doctor may suggest genetic testing (by means of a blood test) of both parents. If you do not have any risk family risk factors, there is a very low chance that genetic analysis will show an abnormality.

ANA testing 

Antinuclear antibodies or ANA are antibodies in your blood that are directed against your cells. These antibodies are often detected in patients with autoimmune diseases. Studies have shown that ANA can also be detected in some patients with RPL, and therefore testing can be considered to explain a possible cause of the pregnancy loss.

Sperm DNA fragmentation 

Doctors have recently started to look at male causes of RPL and there is now some evidence that damaged sperm could increase the risk of pregnancy loss. We still need much more research, but assessing sperm DNA damage could be considered in couples with RPL in order to provide some information on the role of the father in the pregnancy loss.

Which investigations should not be routinely performed?

There are several tests that have been described and carried out in couples with RPL, but do not provide any useful information. This is because:

- they do not provide information on the cause of the pregnancy loss
- they do not help in selecting treatment, and/or
- they do not help in estimating prognosis.

These tests are not routinely recommended for couples with RPL:

- Androgen testing (testosterone)
- Anti-HY antibodies
- Cytokine testing
- HLA determination
- Homocysteine plasma levels
- Insulin resistance testing (diabetes)
- NK cell testing
- Ovarian reserve testing (FSH, AMH, LH, estradiol)
- Prolactin levels (can be measured if you have oligo/amenorrhea)
- Sperm analysis
- Tests for Luteal phase insufficiency (progesterone)
- Vitamin D testing

Although these tests are not recommended for all women with RPL, your doctor may suggest them, based on clinical symptoms (not necessarily related to RPL) or because of your medical or family history.

What are the options for treatment?

> Most couples with RPL have a higher chance of a live birth in their next pregnancy than of having another pregnancy loss, but that does vary depending on maternal age and the number of pregnancy losses and on whether a likely cause has been found.

While some treatments are known to reduce the risk of pregnancy loss in certain circumstances, there is nothing that can remove that risk altogether. This is because treatment for one condition will not prevent a loss caused by something else.

The results of any investigations that you have will help your doctor decide whether or not to recommend treatment.

On pages 10 and 11, we outline the options for treatment of explained RPL. We talk about options for unexplained RPL on page 12

What are the options for treatment of explained RPL?

You have Antiphospholipid syndrome (APS)

→ Treatment with heparin and low-dose aspirin [2] 

There is some research evidence that treatment with heparin and low-dose aspirin increases the chance of a healthy pregnancy in women with three or more pregnancy losses and APS, but there is no evidence regarding women with fewer than three losses. More research is urgently needed. There is also no evidence on whether this treatment is helpful for women with inherited thrombophilia and RPL, or with unexplained RPL.

You have been diagnosed with a thyroid dysfunction

→ Treatment with levothyroxine
(but only if you have very low levels of thyroid hormones) 

There is some research evidence that treatment with levothyroxine reduces the risk of pregnancy loss in women with very low levels of thyroid hormones (this is called clinical hypothyroidism).

If you have less severe hypothyroidism (called subclinical hypothyroidism) or if you have TPO antibodies and a normal thyroid hormone level (see glossary), it is unclear whether levothyroxine treatment would help you. Your doctor should discuss the benefits and risks of treatment with you, and check the function of your thyroid gland (by measuring TSH levels) when you are 7-9 weeks pregnant.

You have a problem with the shape and/or inside of your uterus (uterine malformation)

→ If you have a septate uterus (e.g. where the uterus is divided by a band of tissue [a septum]), you may be offered septum resection within the context of a clinical trial. 

→ If you have other problems in your uterus (such as other uterine malformations, fibroids, polyps or adhesions), surgery is not recommended. For some problems, however, surgery is not feasible. 

Overall, there are very few options to increase your chance of a succesful pregnancy when diagnosed with a uterine malformation. There is very little research evidence to tell us if surgery is of benefit for women with a malformed uterus or for other problems, such as fibroids, polyps and uterine adhesions. There is no evidence that surgery increases the chances of a healthy pregnancy in the future.

[2] Treatment with heparin and low-dose aspirin is recommended for women with APS and 3 or more pregnancy losses. Treatment after 2 losses can be considered in the context of a clinical trial.

Tests showed a genetic abnormality

→ Genetic counselling 

→ Information on the available treatments, including their advantages and disadvantages. 

Genetic counselling is recommended for couples with a genetic abnormality. Genetic counselling includes a discussion of what the test results mean for you and your family, the implications for your baby, and your treatment options. Treatment options include preimplantation genetic diagnosis (PGD, which would be done as part of an IVF procedure) but there is only limited evidence showing a benefit to reduce the risk of another pregnancy loss.

You have tested positive for ANA antibodies

→ No treatments available

There are no specific treatments available for women with RPL and ANA antibodies.

Your partner's sperm showed sperm DNA damage

→ Cessation of smoking, a normal body weight, limited alcohol consumption and a normal exercise pattern is recommended. 

Sperm quality is affected by lifestyle and improving some lifestyle factors, especially diet and exercise, can improve sperm quality. Antioxidants (for men) have not been shown to improve the chances of a live birth. Sperm selection is the selection of sperm with less damage. The benefit of this treatment for couples with RPL and sperm DNA damage is unclear.

If you have, or are found to have an underlying condition, which could possibly be associated with pregnancy loss, your doctor will advise you on treatments for the condition. These treatments may reduce the risk of pregnancy loss. Examples are:

You have PCOS

→ Pituitary suppression before induction of ovulation could be an option 

You have Hyperprolactinemia

→ Bromocriptine treatment 

You have Hyperhomocysteinemia (high levels of homocysteine in your blood)

→ Folic acid and vitamin B6 supplements 

What are the options for unexplained RPL?

If none of the tests show a problem or likely cause of your pregnancy losses, you will be diagnosed as having unexplained RPL.

→ There are no treatments available that are known to improve your chances of a having a baby.

→ It is still advisable to try to live as healthy a lifestyle as possible, with a balanced diet, maintaining a healthy weight, stopping or reducing smoking, avoiding excessive alcohol and avoiding (hard and soft) drugs.

→ Ask your doctor about taking vitamin D supplements.

There is no evidence that vitamin D supplements reduce the risk of pregnancy loss but vitamin D supplementation is frequently prescribed for pregnant women and it may reduce other pregnancy complications.

Treatments that are not recommended.

We note here treatments that we do not recommend for couples with unexplained RPL.
This is either:

- because there is not enough evidence that the treatment reduces the risk of pregnancy loss, or
- because studies have shown that the treatment does not work, or that it might be harmful.

Treatments with insufficient proof (more research is needed/ no proof of safety yet):

- Glucocorticoids/prednisolone (steroids)
- Granulocyte colony-stimulating factor (G-CSF)
- Human chorionic gonadotrophin (hCG)
- ICSI/PGS for Aneuploidy
- Intralipid therapy
- Intravenous immunoglobulin (IvIg)
- Metformin (for women with PCOS)
- Sperm selection

Treatments that do not work for RPL:

- ART, e.g. IUI/IVF/ICSI
- Endometrial scratch
- Vaginal progesterone

Potentially harmful treatments:

- Chinese Herbal treatment
- High-dose[3] folic acid, unless medically indicated
- Lymphocyte immunization therapy

[3] (low-dose folic acid will be prescribed to you for prevention of neural tube defects)

Where can I find more information or support?

More detailed information on each of the topics in this booklet can be found in the clinicians' edition of the guideline on the ESHRE website (www.eshre.eu/guidelines).

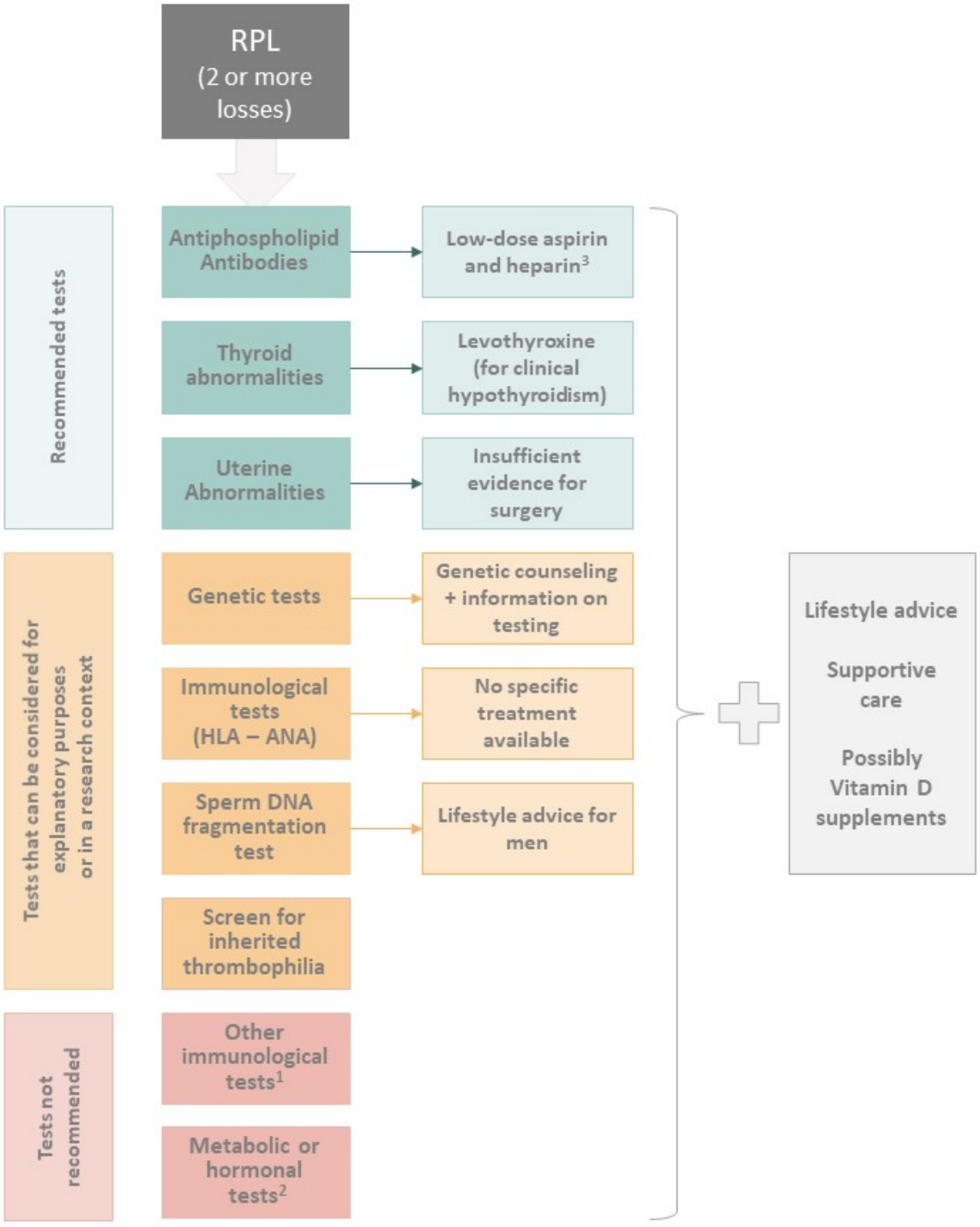
For more detailed information or support, you can contact your doctor or a patient organisation.

In some European countries, there are patient organisations which support couples after pregnancy loss, while in other countries, these patients could find information and support through national patient organisations for infertility.

The Miscarriage Association is a UK organisation that provides support and information for people affected by pregnancy loss. You can find more information at their website https://www.miscarriageassociation.org.uk/ or via info@miscarriageassociation.org.uk.

For contact details of national patient organisations for infertility, you can ask your doctor, or contact Fertility Europe (www.fertilityeurope.eu)

A pictorial summary



1 *Including anti-HY antibodies, Natural Killer (NK) cell testing, anti-HLA antibodies*
2 *Including cytokine testing/polymorphisms, assessment of Polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose, prolactin testing, ovarian reserve testing, luteal phase insufficiency testing, androgen testing, luteinizing hormone (LH) testing, homocysteine plasma levels*
3 *Low-dose aspirin and heparin are recommended after 3 pregnancy losses, or after fewer losses if this is as part of a clinical research trial.*

About this booklet

This booklet aims to involve patients in healthcare improvement by informing them about current standards of care, and by enabling them to make informed decisions on their health, supported by the best available evidence.

1. How this booklet was developed

This booklet was written by Dr Nathalie Vermeulen (methodological expert) and Ruth Bender Atik (patient representative, Miscarriage Association UK), and revised by Dr Mariëtte Goddijn (gynecologist and chair of the Guideline Development Group). Input was also collected from patients and other stakeholders. All the information provided is based on the recommendations in the ESHRE guideline on Recurrent Pregnancy Loss.

2. Who developed the ESHRE guideline?

The ESHRE guideline on Recurrent Pregnancy Loss, was developed by a multidisciplinary guideline development group including gynaecologists, experts in genetics, male fertility, and thrombophilia, a research specialist and a patient representative.

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Nathalie Vermeulen	European Society of Human Reproduction and Embryology

Glossary (explanation of medical or research terms)

Adhesions: Bands of fibrous scar tissue (in the uterus, or elsewhere)

Amenorrhea: The absence of periods in women of reproductive age

Androgens: Male sex hormones, one of which is testosterone.

Antiphospholipid syndrome (APS): An acquired thrombophilic disorder characterised by pregnancy loss and antiphospholipid antibodies in the blood.

Congenital: A congenital disorder, also known as birth defect, is a condition existing at or before birth regardless of cause

Cytokine: A small molecule (protein) produced by a certain cell, which acts on other nearby cells.

DNA: A molecule that carries the genetic instructions to develop and maintain humans (and other organisms).

Down's syndrome: A condition caused by the presence of an extra chromosome (no.21) in a baby's cells. The condition can cause developmental and learning problems.

Fibroids: Abnormal, benign growths of muscle in or on the uterus.

Embryo: A fertilised egg.

Endometrial scratch: A technique where the lining of the uterus is gently 'scratched' which is thought to increase the chance of implantation of the embryo.

Gene: A region of DNA. Each gene determines a feature of a person, what s/he will look like, how s/he will function.

Genetic: Anything related to the genes. (e.g. a genetic error is an error in the genes)

Gestational diabetes: A complication where the women develops diabetes during pregnancy.

Glucocorticoids: A class of steroid hormones that can regulate the immune system. Prednisolone is an example of a glucocorticoid, often used in treatment of immune diseases.

Granulocyte-colony stimulating factor (**G-CSF):** A cytokine that stimulates the bone marrow to produce immune cells and stem cells. In animal studies, it was found to reduce pregnancy loss.

Human chorionic gonadotrophin (hCG): A hormone produced during pregnancy and needed to maintain the pregnancy**.**

Human leukocyte antigen (HLA): A protein that helps the immune cells to react to fragments of infectious organism (viruses) and thus protect the body against infections. Defects in HLA proteins may cause autoimmune diseases.

Homocysteine: A molecule that can be transformed by vitamins to cysteine, a buiding block for proteins in the body.

Hormone: A molecule that is produced by one tissue and carried in the bloodstream to another tissue to cause a biological effect.

HY antibodies: Immune cells against substances encoded by genes on the Y chromosome, which are only present in males. HY Antibodies are found in women after being pregnant with a boy.

Hyperhomocysteinemia: Presence of high levels of homocysteine in the blood, which can be caused by deficiencies of vitamin B6, vitamin B12 or folic acid.

Hyperprolactinemia: Presence of high levels of prolactin, characterised by having no or irregular periods.

Hyperthyroidism: When the thyroid gland produces excessive amounts of thyroid hormones

Hypothyroidism: When there is insufficient thyroid hormone production

Hysterosalpingography: A radiologic procedure (using X-rays) with contrast medium injected in the uterus, used to investigate the shape of the uterus.

In vitro fertilization (IVF): A technique by which eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually one or two resulting embryos are then transferred to the womb. If one of them attaches successfully, it results in a pregnancy.

Infertility: The state of being not fertile and unable to become pregnant, usually defined as not becoming pregnant after 12 months or more of regular unprotected sexual intercourse.

Intralipid therapy: A fat emulsion initially developed as a food supplement, for instance for premature babies, but later found to be useful to treat poisoning. From experiments in mice, it is thought to be able to maintain pregnancy.

Intra-uterine insemination (IUI): A technique where sperm is placed into a woman's womb through the cervix.

Intracytoplasmic sperm injection (ICSI): A special technique in IVF where a single sperm is injected into the egg with a small needle. It is often used when there is insufficient good quality sperm for fertilization by mixing egg and sperm in a dish or test-tube (as with standard IVF).

Intravenous immunoglobulins (Ivlg): A mixture of antibodies (Immunoglobulins) injected (intravenous) in the blood to treat immunological diseases.

Lymphocyte: One type of white blood cells that protect the body against infection.

Oligomenorhea: Infrequent menstruation (4-9 periods per year) in a woman of reproductive age.

Polycystic ovary syndrome (PCOS): A condition characterised by raised levels of androgens and associated symptoms including irregular menstrual periods, heavy periods, excess hair, acne, and difficulty getting pregnant.

Polyps: Abnormal, benign growths attached to a short stalk that protrudes from the inner surface of the uterus.

Pre-eclampsia: A complication of pregnancy characterized by high blood pressure and often a significant amount of protein in the urine.

Pre-implantation genetic diagnosis (PGD): Genetic profiling of embryos before implantation with the aim of selecting embryos that do not carry a specific genetic disease. PGD requires IVF to obtain embryos.

Pre-implantation genetic screening (PGS): Genetic profiling of embryos before implantation with the aim of selecting embryos that will probably not carry any genetic abnormalities. PGS requires IVF to obtain embryos.

Progesterone: A hormone produced by the ovary, but only if ovulation has occurred (after the egg is released). Its action is to prepare the endometrium for implantation of the embryo.

Prolactin: A hormone that emables females to produce milk, but is also involved in many other processes in the body.

Sonohysterography: A procedure by which fluid is inserted into the uterine cavity, and an ultrasound scan is performed at the same time.

Spina Bifida: A birth defect with incomplete closing of the backbone and spinal cord membranes.

Thrombophilia: An abnormality in the clotting of blood, which causes the blood to clot more than it should.

Thyroid gland: A gland, located in the neck that produces several hormones that influence several processes in the body (for instance metabolic rate).

TSH (Thyroid-stimulating hormone): A pituitary hormone that stimulates the thyroid gland

Ultrasound: High frequency sound waves used to provide images of the body, tissues and internal organs.

Disclaimer

The European Society of Human Reproduction and Embryology (ESHRE) developed the current information booklet for patients based on the clinical practice guideline. The aim of clinical practice guidelines is to aid healthcare professionals in everyday clinical decisions about appropriate and effective care of their patients.

This booklet is in no way intended to replace, dictate or fully define evaluation and treatment by a qualified physician. It is intended solely as an aid for patients seeking general information on issues in reproductive medicine.

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