

Number of embryos to transfer during IVF/ICSI

Patient leaflet based on the ESHRE Guideline on the number of embryos to transfer during IVF/ICSI

Introduction

This booklet is addressed to couples and individuals who are planning to achieve pregnancy through IVF/ICSI treatment. For the purposes of this guideline, the guideline development group decided to use the term “women” to design individuals born with a uterus, however, it is not intended to isolate, exclude, or diminish any individual’s experience nor to discriminate against any group. This booklet is intended for patients but may also be useful for their family members and caregivers.

This booklet aims to enhance patients’ understanding of the factors involved in deciding the number of embryos to transfer, ensuring the best chances of a successful outcome while minimising potential risks.

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General introductory statement

This booklet and the information presented are entirely based on the ESHRE Guideline on the number of embryos to transfer during IVF/ICSI (2023). 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 and individuals undergoing ART.

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



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 <https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Embryo-transfer>

Number of embryos to transfer during IVF/ICSI

Why is the number of embryos to transfer important?

Embryo transfer is a crucial step in assisted reproductive technology (ART) where embryos resulting from in vitro fertilisation or intracytoplasmic sperm injection (IVF/ICSI) treatment are transferred to the uterus. The number of embryos transferred plays a significant role in the success and safety of the procedure. It is a balancing act aimed at minimising the safety concerns that are associated with the transfer of multiple embryos for both mother and child without jeopardising the chances of achieving a successful pregnancy.

Understanding elective single (eSET) and double (DET) embryo transfer

During an IVF/ICSI treatment, the fertilisation of multiple eggs may lead to the development of more than one embryo. In the past, oftentimes multiple embryos (more than two embryos) were transferred to the uterus to increase the chances of achieving a successful pregnancy. Improvements in treatment quality have reduced the need to transfer multiple embryos.

Nowadays, the two types of embryo transfer that are mostly used are elective single embryo transfer (eSET), in which only a single embryo is selected and transferred; and double embryo transfer (DET), in which two embryos are selected and transferred to the uterus.

Transferring more than one embryo increases the risk of a multiple pregnancy (twins, triplets), which can have complications for both the mother and the babies. With eSET, only a single embryo, often considered as the best one, is selected from a larger number of available

embryos and transferred to the uterus. The rest of the embryos can be stored and used later in a frozen-thawed embryo transfer (FET).

The guideline development group on the number of embryos to transfer during IVF/ICSI assessed scientific articles related to the choice between single and double embryo transfer and the factors that should be considered during the decision-making process.

Risks associated with multiple pregnancies

What are the medical and psychosocial risks associated with multiple pregnancies?

Multiple pregnancies, such as twins, triplets, or higher-order multiples, carry clear medical risks and complications compared to singleton pregnancies. They can also present psychological challenges and potential risks for both the person expecting and the family. Some of the potential risks associated with multiple pregnancies are summarized in the following two pages.

Healthcare providers, support groups, and mental health professionals can play a vital role in assisting families in managing these challenges and promoting their overall well-being.

You should receive information about:

- **Medical risks related to multiple pregnancy/birth.** (including ectopic pregnancy, preterm birth, low birth weight, pre-eclampsia, placental complications, neonatal intensive care, and long-term developmental issues).
- **Psychosocial risks.** (including increased stress levels, emotional adjustment difficulties, postpartum depression, parental bonding difficulties and social isolation associated with multiple pregnancies).
- **Financial strain and costs.**



You should be referred for a detailed discussion on the non-clinical factors to consider if deciding on the number of embryos to transfer during IVF/ICSI.



Medical risks associated with multiple pregnancies

FOR THE MOTHER

Ectopic pregnancy

The rate of ectopic pregnancies and associated risks are higher following the transfer of multiple embryos. Those risks include the implantation outside the uterus, multiple gestational sacs and fallopian tube damage. Ectopic pregnancies can be challenging to diagnose, and their treatment often requires medical interventions such as medication or surgery.

Gestational diabetes

The risk of developing gestational diabetes is higher in multiple pregnancies. This condition can have short-term and long-term health consequences for both the mother and the babies.

Preeclampsia

Multiple pregnancies increase the risk of developing preeclampsia. Preeclampsia can be life-threatening for the mother and can affect the growth and well-being of the babies.

Placental complications

Multiple pregnancies are associated with a higher risk of placental complications, such as placental abruption, placenta previa, and abnormal placental development. These conditions can lead to bleeding, preterm birth, and compromised fetal well-being.

FOR THE BABY

Preterm birth

Multiple pregnancies have higher risk of preterm birth. Premature babies may face health issues due to their underdeveloped organs and may require specialised medical care.

Low birth weight

Babies from multiple pregnancies are more likely to have low birth weight. Low birth weight infants may have difficulties with growth, development, and an increased risk of health problems.

Neonatal intensive care

Babies from multiple pregnancies are more likely to require care in the neonatal intensive care unit (NICU) due to prematurity, low birth weight, and other complications. NICU care involves specialised medical attention and can be emotionally and financially demanding for families.

Long-term developmental issues

Multiple pregnancies may increase the risk of long-term developmental issues in children, including cognitive impairments, learning disabilities, and behavioural challenges.

Selective embryo reduction

In cases where more than two embryos implant into the uterus (triplets, quadruplets, etc....), physicians may opt to perform selective embryo reduction to a twin or singleton pregnancy in order to reduce the risks. The resulting pregnancies still have higher chances of some of the abovementioned complications, compared with pregnancies that start as twin or singleton ones.



Psychosocial risks of multiple pregnancies

INCREASED STRESS LEVELS

The prospect of carrying and raising multiple babies simultaneously can lead to heightened stress levels.

The demands of multiple pregnancies, combined with concerns about the health and well-being of both the mother and babies, can contribute to elevated stress and anxiety.

POSTPARTUM DEPRESSION

The risk of depression after giving birth can be higher in multiple pregnancies compared to singletons.

The challenges of caring for multiple infants, sleep deprivation, and the physical demands of recovering from a multiple pregnancy and birth can contribute to increased vulnerability to postpartum depression.

PARENTAL BONDING DIFFICULTIES

Bonding with multiple babies simultaneously can be challenging for parents of multiples.

Limited time and resources, as well as divided attention, can affect the parent-infant bonding process.

This can lead to feelings of guilt, frustration, and concerns about forming strong individual connections with each child.

EMOTIONAL ADJUSTMENT DIFFICULTIES

Adjusting to the idea of multiple babies and the associated responsibilities can be emotionally overwhelming for expectant parents.

The anticipation of caring for multiple infants simultaneously, managing their needs, and the potential impact on family dynamics may trigger feelings of anxiety, fear, and inadequacy.

FINANCIAL STRAIN

Raising multiple children simultaneously can place a significant financial burden on families.

The costs associated with healthcare, childcare, education, and other essential needs can be substantial, which may lead to financial stress and strain on the family's well-being.

SOCIAL ISOLATION

Caring for multiple babies can be isolating, as the demands of round-the-clock care and the logistical challenges of managing multiple children can limit social interactions and support systems.

This can lead to feelings of social isolation and a reduced sense of community.



Success rate measure following SET and DET

How do fertility specialists measure the chances of live birth?

There are two different ways of doing this. In a typical IVF/ICSI cycle, several egg cells are obtained, leading to more than one embryo. The success rate in terms of live births (birth of at least one living child) can be calculated as follows:

- For each separate embryo transfer cycle, called the live birth rate. These provide a snapshot of success for a specific transfer.
- For the whole group of embryos, called the cumulative live birth rate. Cumulative live birth rates show the overall chance of live birth.

For example, for patients having 4 embryos, the average live birth rate for each embryo transfer cycle might be 18% but the cumulative live birth rate after transferring all 4 embryos might be as high as 75% (this is an example only; please discuss your specific chances with your fertility specialist). Cumulative live birth rate provides a more comprehensive and realistic measure of success in ART, as it considers the effect of multiple treatments and accounts for potential failures and subsequent attempts to achieve a live birth.

Is eSET as successful as DET in terms of live birth?

The success of eSET compared to DET in terms of live birth rates can vary but cumulative live birth rates are usually similar or higher with eSET. The goal of eSET is to achieve a healthy singleton pregnancy while reducing the risk of pregnancy and offspring complications.

Factors to be considered during the decision-making process

Which clinical factors could your caregivers consider during an IVF/ICSI treatment? Does any of these factors necessitate eSET or DET?

It is essential to discuss your individual chances and risks with your fertility specialists. They will consider your individual factors and context to provide personalised advice on whether eSET or DET is the most suitable approach for you. The decision should be made after carefully weighing the chances of success and the risks associated with multiple pregnancies. Please bear in mind that in many countries, the number of embryos to transfer is strictly regulated because of the importance to minimise pregnancy-related complications.

Maternal age, embryo quality, reproductive and medical history, previous IVF cycles outcomes, and previous response to fertility treatment should not be considered as factors to apply DET instead of eSET.



It is important to have a detailed discussion with your fertility specialists to understand how these factors in conjunction with your preferences and values, can affect the decision on the number of embryos to transfer.



Factors affecting decision making during ART treatment

It is essential to discuss your individual chances and risks with your fertility specialist.

FEMALE AGE

Fertility declines with advanced female age.

Patients younger than 38 years have higher or similar cumulative live birth rates after elective single embryo transfer (eSET), compared with double embryo transfer (DET). They also have much higher multiple pregnancy rates after DET.

Only eSET should be performed for this age category.

Patients aged 38 years or more have similar cumulative live birth rates and multiple pregnancy rates after eSET and DET. However, advanced female age is associated with increased risk of chromosomal problems in embryos. As a result, older patients may have a lower chance of success. As age increases, however, the rates of pregnancy complications also increase. This is why the guideline development group considers that patients over the age of 38 years also benefit from eSET.

QUALITY OF EMBRYOS

Embryo quality is an essential factor in determining the success of treatment. Embryos are graded based on factors such as their cell number, cell symmetry, and degree of fragmentation.

High-quality embryos have a better chance of implantation and their success rate with eSET is comparable to, or even higher, than DET.

OVARIAN RESPONSE

The decision on how many embryos to transfer is based on embryo numbers and quality and not on ovarian response. Sometimes, fertility specialists may decide to postpone embryo transfer for a later time and freeze all embryos, such as in cases of high ovarian response (too many ovarian follicles developing), there may be a risk of severe ovarian hyperstimulation syndrome (OHSS), which is potentially life-threatening.

OUTCOME OF PREVIOUS IVF/ICSI TREATMENTS

If a person has undergone previous IVF cycles, the outcomes and response to treatment can provide valuable information for future treatments. However, repeated failed cycles alone do not necessitate a transfer of more than one embryo at a time.

DURATION OF INFERTILITY

A longer duration of infertility can mean a more difficult underlying problem. However, this factor alone should not call for DET.

PATIENT PREFERENCES AND VALUES

The individual's personal preferences and values are important. Some individuals may have a strong preference for minimising the risk of multiple pregnancies and opt for elective single embryo transfer (eSET). While others may have personal reasons for accepting the increased risks and choose to transfer multiple embryos.



Is eSET more expensive than DET?

ART treatments are expensive, which is why costs are an important part of treatment planning. In many countries, patients pay for ART treatments whilst treatments of pregnancy and neonatal complications is covered by the national health insurance.

Studies comparing the cost-effectiveness of eSET and DET have shown varying results. However, including obstetric and neonatal costs into the analysis consistently indicates that DET is associated with higher costs compared to eSET. Indirect costs, such as sick leaves and absence from work, also contribute to the overall expenses after DET and multiple pregnancies.

Population-based studies have demonstrated that eSET is generally less expensive than DET. Furthermore, singleton pregnancies conceived through ART are associated with lower obstetric and paediatric costs compared to twins.

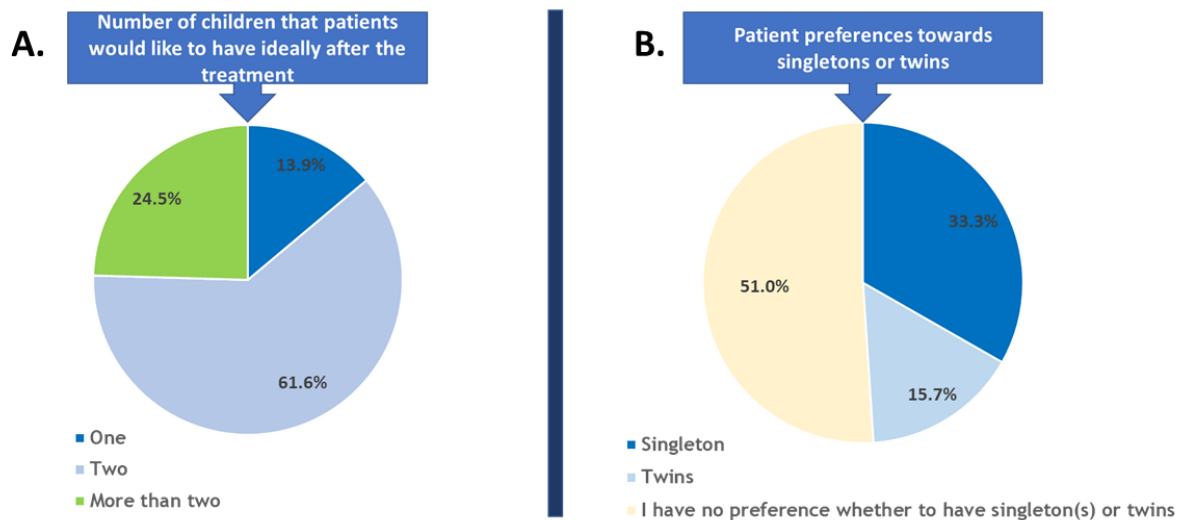
You should discuss the cost-related information with your fertility specialists at the treatment planning stage.



How can you and your caregiver come to a shared decision regarding the number of embryos to transfer?

ART is a procedure aimed at overcoming obstacles in family building. However, research on patient preferences regarding the number of embryos to transfer has often neglected the family building element. To address this, a survey was conducted in multiple languages to understand patients' wishes and beliefs regarding family building and pregnancy (figure 4). The survey revealed that most patients (85.6%) desired to have more than one child. While half of the patients had no preference between singletons and twins, among those who did, singletons were more preferred (67.9% vs. 32.1%). Preference for twins was mainly driven by the desire to have several children quickly (49.5%), fondness for twins (41.7%), and avoiding multiple hormonal stimulations of the ovaries (31.5%). Results from the survey are included in the guideline recommendations for fertility treatment practitioners.

Patients' preferences. **A.** Ideal number of children that patients would like to have after the treatment. **B.** Patients preferences towards singletons or twins.



The guideline development group reminds fertility specialists that shared decision-making is recommended. This involves counselling and information sharing between caretakers and patients to ensure accurate and transparent information is provided to patients regarding treatment success rates and risks associated with multiple embryo transfers and multiple pregnancies. At the same time, it ensures that patient wishes and preferences are understood and implemented if possible.

Decision aids have been developed to promote shared decision-making, providing information about pregnancy chances, complication rates, and available options. Scientific evidence shows that such information increases the desirability of eSET and decreases the appeal of DET.

During counselling, patient and couples' attitudes and knowledge should be considered. One person may require more involvement and information in deciding to transfer a single embryo, while another one may be more aware of the risks but find the decision more challenging.

Overall, shared decision-making helps patients and fertility specialists reach agreements on the number of embryos to transfer, taking into account patient preferences, treatment success rates, and the risks associated with possible complications and multiple pregnancies.

You should be offered comprehensive information regarding treatment success and complications rates in order to reach a decision together with your fertility practitioner on the number of embryos to transfer.



Other strategies for embryo transfer

Are there any other options for embryo transfer apart from eSET and DET?

Yes, for example TET (triple embryo transfer) and compulsory SET (single embryo transfer).

TET involves the transfer of three embryos to the uterus. It is a less common approach compared to eSET and DET. TET was used in earlier years of ART treatments, when success rates were lower. The goal of TET is to increase the chances of achieving a pregnancy; however, it carries an extremely high risk of multiple pregnancy associated with many complications. Due to this, TET is no longer recommended.

Compulsory SET is when a single embryo is transferred because of a specific legislative or clinic-specific policy or may be based on factors such as age, embryo quality or the presence of underlying medical conditions.

Transfer of more than two embryos is not recommended.



Egg/embryo donation and gestational carriers

Should eSET or DET be performed after egg or embryo donation?

Pregnancies that start from egg or embryo donation carry a much higher risk of complications, even if the person carrying the child is young and healthy. This is why eSET should always be performed in this type of treatments.

Only eSET should be performed for patients undergoing ART with donor eggs or embryos.



Should eSET or DET be performed in gestational carriers?

A gestational carrier, also known as a surrogate mother or gestational surrogate, is a woman who carries and gives birth to a baby for another individual or couple. A gestational carrier is therefore not biologically related to the baby she carries. The embryo implanted in the gestational carrier's uterus is derived from genetic material of the intended parents or donors through IVF techniques. These pregnancies also have higher risks of complications for both the carrier and the offspring. eSET should always be performed in this type of treatments.

Only eSET should be performed for gestational carriers.



Where can I find more information or support?

More detailed information on each of the topics in this booklet can be found in the fertility specialists' edition of the guideline on the ESHRE website (<https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Embryo-transfer>)

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

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

Pictorial Summary - The benefits of transferring only one embryo at a time



About this booklet

This booklet aims to involve patients in healthcare improvement by informing them about the best possible outcomes while prioritising their safety and well-being. Patients should be enabled to make informed decisions on their health, supported by the best available evidence and to openly discuss any concerns or questions they may have with their fertility specialist.

How this booklet was developed

This booklet a patient leaflet written by Dr Zdravka Veleva (chair of the guideline development group), Klaudija Kordic (chairperson of Fertility Europe and patient representative within the guideline development group), and Dr Saria Mcheik (methodologist and research specialist). Input was also collected from patients and other stakeholders. All the information provided is based on the recommendations in the ESHRE guideline on the number of embryos to transfer during IVF/ICSI.

Who developed the ESHRE guideline?

The ESHRE guideline on the number of embryos to transfer during IVF/ICSI was developed by a multidisciplinary guideline development group including six clinicians, six embryologists, one psychologist, one ethics expert, two research specialists and two patient representatives.

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Glossary (explanation of medical or research terms)

Assisted reproductive technologies (ART): medical procedures or techniques that are used to assist individuals or couples in achieving pregnancy when they are facing difficulties conceiving naturally. IVF, ICSI, frozen embryo transfer, and intrauterine insemination are types of ART.

Compulsory single embryo transfer: the transfer of the only embryo available for transfer.

Double embryo transfer: the transfer of two embryos in an ART procedure.

Ectopic pregnancy: also called extrauterine pregnancy. A pregnancy resulting from the implantation of an embryo outside the uterine cavity. Ectopic pregnancies are dangerous for the life of the pregnant person and do not lead to a live birth of a healthy baby.

Egg donation: the use of eggs from an egg donor for reproductive purposes or research.

Elective single embryo transfer (eSET): the transfer of one (a single) embryo selected from a larger group of available embryos.

Embryo: the initial form of development of the fertilised egg. It is formed after the fertilised egg's first division. The embryo develops and grows further until eight completed weeks after fertilisation, which is equivalent to 10 weeks of pregnancy. After this, it is called a foetus.

Embryo donation (for reproduction): patients can donate an embryo that was made from their egg and/or sperm cell to other patients.

Embryo fragmentation: small parts (fragments) of cells that can be seen by microscope just next to the embryo cells.

Embryo transfer (ET): placement into the uterus of an embryo from day 1 to day 7 after fertilisation by IVF or ICSI.

Embryo transfer cycle: an ART cycle in which one or more fresh or frozen-thawed embryos are transferred into the uterus.

Gestational carrier: a woman who carries a pregnancy with an agreement that she will give the offspring to the intended parent(s). Egg cells or sperm cells can originate from the intended parent(s) and/or a third party (or parties). This replaces the term 'surrogate.'

Gestational diabetes: a type of diabetes that occurs during pregnancy and is characterised by high blood glucose (sugar) levels. This condition can have short-term and long-term health consequences for both the mother and the offspring.

Gestational sac: A fluid-filled structure of an early pregnancy, which may be located inside or, in the case of an ectopic pregnancy, outside the uterus. It usually contains an embryo.

Gonadotropins: Hormones that stimulate the ovaries or testes. They are used in fertility treatment to stimulate follicle growth or to induce ovulation.

Higher-order multiple pregnancy: a pregnancy with more than three embryos or foetuses.

Implantation: during implantation, the embryo first attaches and then burrows into the uterine lining. Implantation starts 5 to 7 days after fertilisation of the egg and results in the formation of a gestation sac. In case of an ectopic pregnancy, implantation develops into tissue outside the uterine cavity, for example into the fallopian tubes.

Intracytoplasmic sperm injection (ICSI): an IVF technique in which fertilisation occurs when a single sperm cell is introduced into an egg cell.

In vitro fertilisation (IVF): fertilisation of an egg cell by a sperm cell outside of the body. The term IVF has two uses. In the stricter sense, IVF means the method of fertilising an egg cell by placing a droplet of sperm cells nearby. The term IVF can also be used in a broader sense to include all methods of fertilisation outside the body, including ICSI, and in these cases is often also abbreviated as IVF/ICSI.

Infertility: a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner. Infertility can be diagnosed after a shorter time interval based on medical, sexual and reproductive history, age, physical findings and diagnostic testing.

Infertility counselling: A professional intervention with the intention to mitigate the physical, emotional and psychosocial consequences of infertility.

IVF/ICSI: please see IVF (broader meaning).

Live birth: the birth of a living child after 22 completed weeks of pregnancy, or if birth weight is at least 500 grams.

Live birth rate: The success rate in terms of live births (birth of at least one living child) can be calculated in two ways:

- For each separate embryo transfer cycle, called the "live birth rate". These provide a snapshot of success for a specific transfer.
- For the whole group of embryos available for transfer before freezing, called the "cumulative live birth rate". Cumulative live birth rates show the overall chance of live birth.

Low birth weight: birth weight less than 2500 g. Low birth weight infants may have difficulties with growth, development, and an increased risk of health problems.

Multiple birth: the birth of more than one baby at a time, such as twins, triplets etc.

Ovarian hyperstimulation syndrome (OHSS): a group of complications that can occur when the ovaries are overstimulated, such as swollen and painful ovaries, nausea, vomiting and dehydration, accumulation of liquid into the abdomen and chest, formation of blood clots in the legs or lungs. Severe OHSS can be a life-threatening condition.

Ovarian response: ovarian response to gonadotropin stimulation refers to how the ovaries react, i.e. how many follicles develop and how many eggs are collected, during the administration of fertility drugs called gonadotropins during IVF/ICSI treatment.

Ovarian stimulation: medical treatment that induces the development of mature egg cells that can be used in ART.

Placenta praevia: placenta covering the lower uterine segment including the uterine cervix and thus presenting a partial or complete obstacle to vaginal birth. Patients with placenta praevia may experience profuse bleedings from the placenta, which can jeopardise the continuation of the pregnancy.

Placental abruption: untimely separation of the placenta from the inner lining of the uterus during the pregnancy. Placental abruptions are medical emergencies because of the risk of imminent pregnancy demise.

Pre-eclampsia: a pregnancy condition characterised by high blood pressure and damage to organs, such as the liver and kidneys. Pre-eclampsia can be life-threatening for the mother and offspring and can also affect the growth and well-being of the baby.

Preterm birth: a birth that takes place after 22 weeks and before 37 completed weeks of pregnancy. Premature babies may face health issues due to their underdeveloped organs and may require specialized medical care.

Selective induced embryo/foetal reduction: a medical intervention that selectively aborts one or more (but not all) gestational sacs or embryos/foetuses from the uterus in a multiple pregnancy.

Single embryo transfer (SET): the transfer of one embryo in an ART procedure. There are different types of SET, for example elective single embryo transfer (eSET) and compulsory single embryo transfer.

List of figures

Figure 1 Medical risks associated with multiple pregnancies for the mother and the baby.

Figure 2 Psychosocial risks associated with multiple pregnancies.

Figure 3 Clinical factors to consider when deciding on the number of embryos to transfer.

Figure 4 Patients' preferences. A. Ideal number of children that patients would like to have after the treatment. B. Patients preferences towards singletons or twins.

Figure 5 The benefits of transferring only one embryo at a time.

General 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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