





Coláiste na hOllscoile Corcaigh



### Artificial Reproductive Technology Desirable / Undesirable Outcomes

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19<sup>th</sup> October 2024



UCD Radiography & Diagnostic Imaging

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Definition of infertility

What is Artificial Reproductive Technology (ART)

History of ART

Complications of ART including early pregnancy – immediate, short term and long term seen on ultrasound





Infertility has defined as a

"A disease characterised 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 as a couple"

European Society of Human Reproduction and Embryology (2021)

# Artificial Reproductive Technology





An Intrauterine Insemination (IUI) cycle refers to steps in a process that involves:

- Ovarian stimulation
- Semen prep in a laboratory
- Transferring resulting prepared sample of sperm to the female reproductive tract



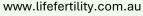
www.babycentre.com.au

# Artificial Reproductive Technology

An Invitro Fertilisation (IVF) and an Intracytoplasmic Sperm Injection (ICSI) cycle refers to steps in a process that involves:

- Ovarian stimulation
- Surgical removal of eggs from the ovary
- Fertilization with sperm in a laboratory
- Transferring resulting embryo(s) to the female reproductive tract











www.vitrolife.com



#### Ultrasound has been fundamental in the advancement of ART treatments

Ultrasound is used for the assessment of the sub-fertile woman,

monitoring ovarian response to medication with follicle tracking scans,

oocyte retrieval, embryo transfer, assessment of early pregnancy and the

treatment of complications of ART including in early pregnancy







#### The Lancet

Volume 302, Issue 7831, 29 September 1973, Pages 728-729



Letters to the Editor

# TRANSFER OF A HUMAN ZYGOTE

D. De Kretzer, P. Dennis, B. Hudson, J. Leeton, A. Lopata, K. Outch, J. Talbot, C. Wood

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### https://doi.org/10.1016/S0140-6736(73)92553-1









### Human Fertility, September 2009; 12(3): 137-143

#### Thirty years of IVF: The legacy of Patrick Steptoe and Robert Edwards

#### PETER R. BRINSDEN

Consultant Medical Director, Bourn Hall Clinic, Cambridge, UK

#### Abstract

In this article, the author presents a review of the early collaboration between Patrick Steptoe and Robert Edwards, gynecologist and scientist, which ultimately led to the birth of Louise Brown in 1978, the first baby to be born as a result of *in-vitro* fertilisation. Following this momentous event, the author shows how Steptoe and Edwards continued to influence further developments in the treatment of infertile couples, both in the United Kingdom and Worldwide.

Keywords: In-vitro fertilisation (IVF), IVF treatment

Pioneering work by Robert Edwards, Patrick Steptoe and Jean Purdy in the development of IVF





'This is not the beginning of the end, but only the end of the beginning'

Patrick C Steptoe, Quote from the Press Conference following the birth of Louise Brown, 25 July 1978

Edwards and Steptoe were awarded the Nobel Peace Prize for Physiology or Medicine 'for the development of in vitro fertilisation' in 2010 A History of IVF





#### 1978 – Birth of Louise Brown - worlds first IVF Baby

1984 – Birth of first Frozen Embryo Transfer Baby

1986 – Birth of First Babies born using Frozen Oocytes

1992 – Birth of First ICSI Baby





#### 1978 First IVF Baby UK

Natural menstrual cycle

Laparoscopic retrieval of a single preovulatory follicle

Fertilised in vitro

Single embryo transferred

1981 First IVF Baby USA

Ovaries stimulated with human menopausal gonadotropin induced the development of several follicles to produce oocytes (controlled ovarian stimulation)

Laparoscopic retrieval of pre-ovulatory oocytes

Fertilised in vitro

Cleavage stage embryos transferred





FERTILITY AND STERILITY Copyright 4 1980 The American Fertility Society

Vol. 33, No. 2, February 1980 Printed in U.S.A.

#### PREGNANCY FOLLOWING INTRAUTERINE IMPLANTATION OF AN EMBRYO OBTAINED BY IN VITRO FERTILIZATION OF A PREOVULATORY EGG

ALEXANDER LOPATA, M.B., B.S., Ph.D.\* IAN W. H. JOHNSTON, M.B., B.S., M.G.O., F.R.C.O.G., F.AUST.C.O.G.† IAN J. HOULT, M.B., B.S., M.R.C.O.G.† ANDREW I. SPEIRS, M.B., B.S., M.R.C.O.G., F.AUST.C.O.G.†





A normally progressing pregnancy has been established by implanting an eight-cell embryo into the uterine cavity of an infertile woman. The embryo was obtained by in vitro fertilization of a preovulatory egg aspirated at laparoscopy 28 hours after the beginning of the luteinizing hormone surge during the patient's natural menstrual cycle. Elevated levels of serum human chorionic gonadotropin and progressively increasing levels of total urinary estrogens and pregnanediol confirmed the presence of an early pregnancy. Ultrasound examination revealed an intrauterine gestational sac at 5 weeks, a 1-cm fetus with fetal heartbeat at 7 weeks, and an active, normally growing fetus at 13 and 16 weeks. Chromosome analysis at this time revealed no abnormality, and the  $\alpha$ -fetoprotein level was within normal limits. The patient is due to be delivered on or about June 28. Fertil Steril 33:117, 1980

First report of successful ultrasound-guided oocyte retrieval – Copenhagen 1981





Letters to the Editor

COLLECTION OF HUMAN OOCYTES FOR IN VITRO FERTILISATION BY ULTRASONICALLY GUIDED FOLLICULAR PUNCTURE

Suzan Lenz, J.Glenn Lauritsen, Merete Kjellow

https://doi.org/10.1016/S0140-6736(81)92335-7





• First Oocyte retrievals was performed by laparoscopy

• Associated risks of general anaesthetic, surgery and post operative risks





### Implantation rates

The Early Days

< 5 % per embryo transferred

► Aggressive ovarian stimulation protocols

Increasing the number of embryos transferred into the uterus

### **Desired Outcome**







# Complications of Artificial Reproductive Technology





### Immediate:

- Infection
- Haemorrhage
- Ovarian Hyperstimulation Syndrome
- Ovarian Torsion

### Short Term:

- Ovarian Hyperstimulation Syndrome
- Risks of early pregnancy

## Long Term:

• Risks of multiple pregnancy

#### Sullivan-Pyke et al, (2017)

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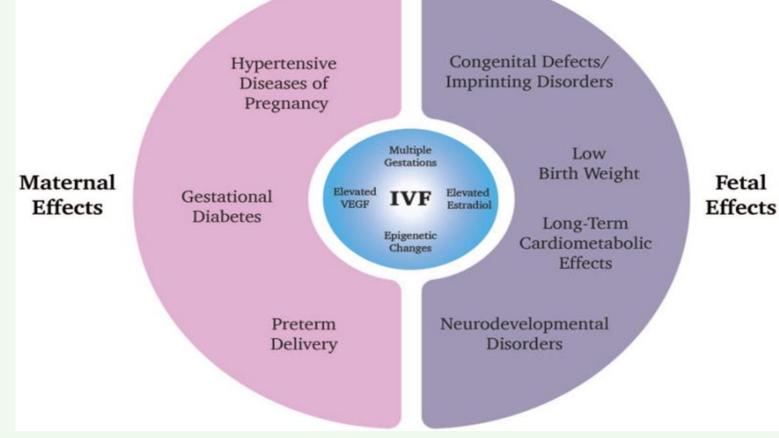


Figure 1. Summary of adverse maternal and fetal affects associated with IVF



Adverse maternal outcomes associated with IVF include hypertensive diseases of pregnancy, gestational diabetes, and preterm delivery.

Fetal effects include low birth weight, congenital defects/imprinting disorders, as well as potentially neurodevelopmental disorders and long-term cardiometabolic effects.

The risk of multiple gestations in IVF pregnancies is the main driver for these outcomes, but other mechanisms are actively being investigated.

Features of IVF including hormonal stimulation that leads to increased oestradiol and VEGF levels may contribute.

Epigenetic alterations in imprinted genes after hormonal stimulation and embryo culture may also be a driver for some of these adverse outcomes.





Involves the collection of eggs from the ovarian follicles using a needle under the guidance of transvaginal ultrasound

Complications of Oocyte retrieval include:

- Blood vessel injury
- Bowel perforation
- Ureteric injury
- Introduction of infection into the pelvis or abdomen

Rate of complications post OR 0.4% (Levi-Setti et al, 2018)

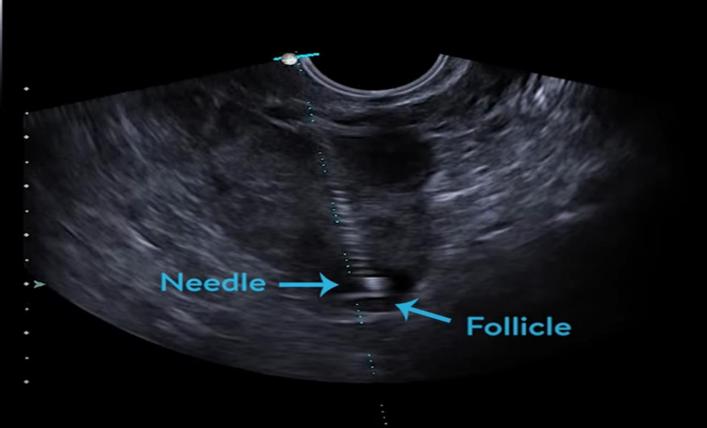


















### www.fertilitywa.com.au





### Infection

Detailed medical history prior to starting controlled ovarian stimulation

Identification of those women with comorbidities

Identification of at-risk groups (immunocompromised, diabetics, severe endometriosis, history of multiple surgeries)

Use of prophylaxis antibiotics in this group

## Haemorrhage



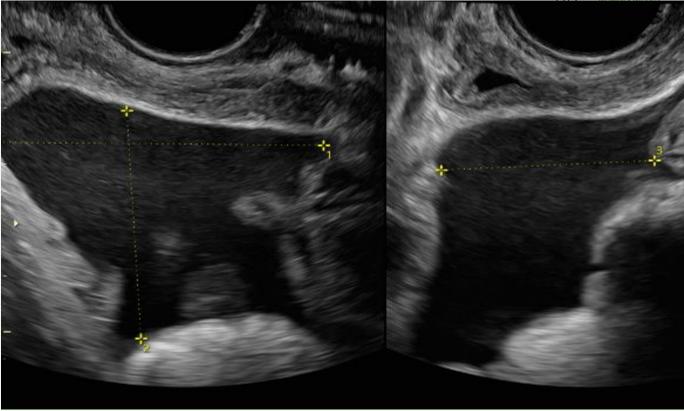


Oocyte retrieval is performed using Trans Vaginal Ultrasound

- Procedural risk of haemorrhage
- Limit the number of vaginal punctures to two where possible
- Use of ultrasound to identify peripheral follicles prior to puncture and aspiration
- Use of colour Doppler to identify blood vessels







# **Ovarian Hyperstimulation Syndrome (OHSS)**





Ovarian hyperstimulation syndrome (OHSS) is an latrogenic condition

It is a complication that can occur in assisted reproductive technology treatments

Characterized by an abnormally high response of the ovary to the medication administered, especially in *in vitro* fertilization

Excessive growth of ovarian follicles

Accumulation of fluid in the abdominal and lung cavities

A water imbalance in the body





Incidence of OHSS:

Death due to OHSS is rare, with a mortality rate estimated at 1:400 000– 1:500 000 stimulated cycles (Brindsen et al,1995)

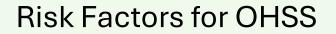
0.4 % incidence of Ovarian Hyperstimulation Syndrome reported by the European IVF- monitoring consortium in 2016 (De Geyter et al, 2020)







www.invitra.com







IVF / ICSI treatment with controlled ovarian stimulation

Polycystic Ovarian Syndrome (PCOS)

High AMH ( > 30)

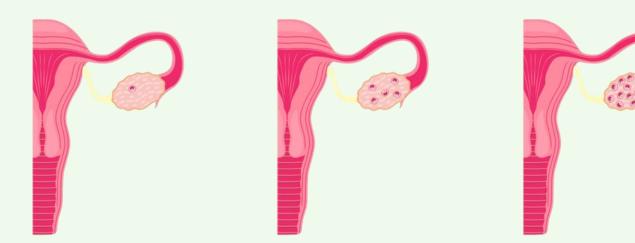
Age (<35)

Low BMI

Previous ART cycle with OHSS







Natural Ovulation

**Controlled Stimulation** 

Ovarian Hyperstimulation

https://www.lifecell.in

# Signs and Symptoms of OHSS

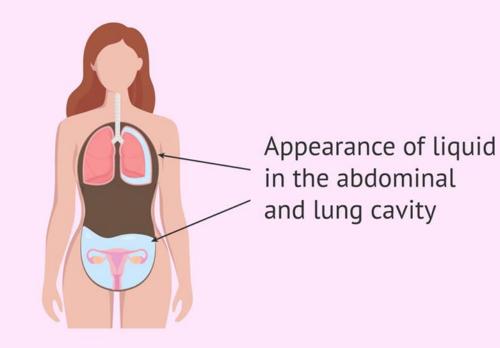


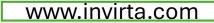


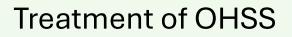
- Severe abdominal pain
- Bloating with enlarged abdomen
- Rapid weight gain
- Severe nausea and vomiting
- Decreased urinary output
- Shortness of breath
- Symptoms of DVT/PE
- Increased ovarian size on ultrasound with large areas of adnexal free fluid















Identify those women at risk of OHSS

Use of GnRH agonist for final oocyte maturation

Cancel cycle post oocyte retrieval, cryopreserve embryos and plan Frozen Embryo Treatment cycle

Use of carbergoline (Dopamine agonist) 0.5mgs/day for 5 to 7 days to those women at risk of OHSS

Use of antagonist protocol for those women at risk of OHSS for secondary prevention of severe OHSS

Use of venous thromboembolism prophylaxis for women who develop OHSS

Human Reproduction Open, pp. 1–13, 2020 doi:10.1093/hropen/hoaa009

doi:10.1093/nropen/noaa009

human reproduction open

#### **ESHRE PAGES**

# ESHRE guideline: ovarian stimulation for IVF/ICSI<sup>†</sup>

The ESHRE Guideline Group on Ovarian Stimulation, Ernesto Bosch<sup>1</sup>, Simone Broer<sup>2</sup>, Georg Griesinger<sup>10,3</sup>, Michael Grynberg<sup>4</sup>, Peter Humaidan<sup>5</sup>, Estratios Kolibianakis<sup>6</sup>, Michal Kunicki<sup>7</sup>, Antonio La Marca<sup>8</sup>, George Lainas<sup>10,9</sup>, Nathalie Le Clef<sup>10,10</sup>, Nathalie Massin<sup>11</sup>, Sebastiaan Mastenbroek<sup>12</sup>, Nikolaos Polyzos<sup>13</sup>, Sesh Kamal Sunkara<sup>14</sup>, Tanya Timeva<sup>15</sup>, Mira Töyli<sup>16</sup>, Janos Urbancsek<sup>17</sup>, Nathalie Vermeulen<sup>10,10</sup>, and Frank Broekmans<sup>10,2,\*</sup>

#### Prevention of OHSS

Which GnRH agonist medication as a method of triggering will add to the prevention of OHSS also with regards to overall efficacy

A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS



Is the freeze-all protocol meaningful in the prevention of OHSS also with regard to efficacy?

A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS





Figure 1 Schematic overview of the guideline 'ovarian stimulation for IVF/ICSI'. AMH: anti-Müllerian Hormone; AFC: antral follicle count; rFSH: recombinant FSH; p-FSH: purified FSH; hp-FSH: highly purified FSH; LPS: luteal phase support, ET: embryo transfer.













#### **Ovarian Torsion**





- Ovarian/ Adnexal torsion is a rare complication in ART
- Gynaecological emergency
- Incidence 0.025% 0.2% (Smith et al 2010)

Predisposing factors include

Increased ovarian size
Mobile ovary
Long pedicle

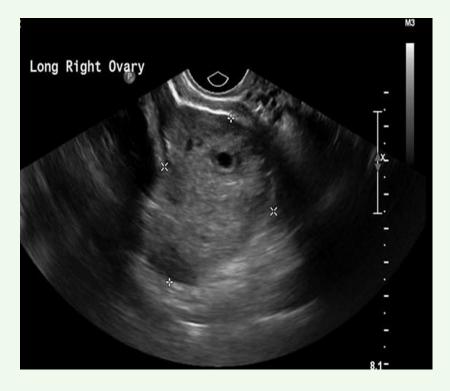




Ultrasound appearances:

# Asymmetric enlargement of the twisted ovary

Enlarged and oedematous ovarian stroma with peripherally displaced follicles



#### Miscarriage / Pregnancy Loss





Miscarriage is generally defined as the spontaneous loss of a pregnancy before it reaches viability

Early pregnancy miscarriage is a non-viable intrauterine pregnancy less than 13 weeks estimated gestation age

Most common complication of early pregnancy

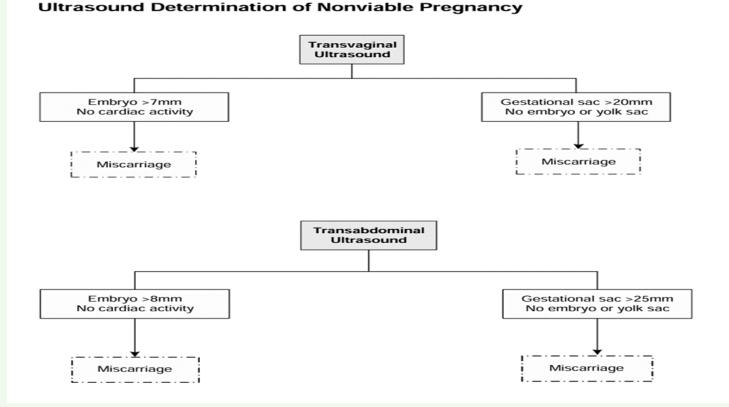
Prevalence - up to 25 % of pregnancies





Governing Body	Recommendations				
	Embryo >5 mm and absent fetal cardiac activity				
The Society of Gynecologists of Canada (SGOC) (21)	Intrauterine mean gestational sac diameter >8 mm with absent yolk sac				
	Intrauterine mean gestational sac diameter >16 mm without fetal pole				
The American College of Radiologists (ACR) (22)	Embryonic crown-rump length >5 mm and absent fetal cardiac activity				
Royal College of Obstetricians and Gynaecologists (RCOG) and	Intrauterine gestational sac with mean diameter ≥ 20 mm and no yolk sac				
Royal College of Radiologists (RCR) (23)	Fetal crown-rump length ≥ 6 mm with absent fetal cardiac activity				
Australasian Casiato fay I Itrasound in Madisina (ACI IMA (24)	Mean gestational sac diameter ≥ 20 mm with absent embryonic structures				
Australasian Society for Ultrasound in Medicine (ASUM) (24)	Embryonic crown-rump length ≥ 6 mm with absent fetal heart rate				
Institute of Obstetricians and Gynaecologists, Royal College of	Mean gestational sac diameter >20 mm with absent embryonic structures (embryo or yolk sac)				
Physicians of Ireland (25)	Embryonic crown-rump length ≥ 7 mm with absent fetal heart rate				

## Ultrasound Determination of Nonviable Pregnancy (HSE 2012)



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#### **Ectopic Pregnancy**





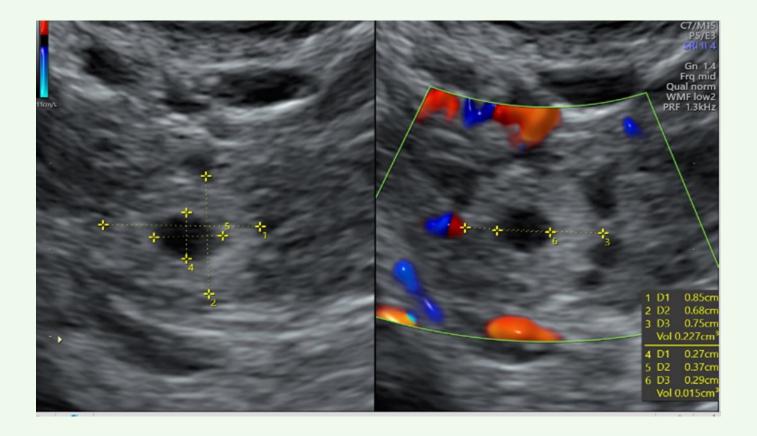
Ectopic pregnancy refers to a pregnancy that develops outside the uterine cavity

- Fallopian Tube
- Cervical ectopic
- Ovarian ectopic
- Caesarean scar ectopic
- Interstitial pregnancy
- Abdominal ectopic

#### **Ectopic Pregnancy**



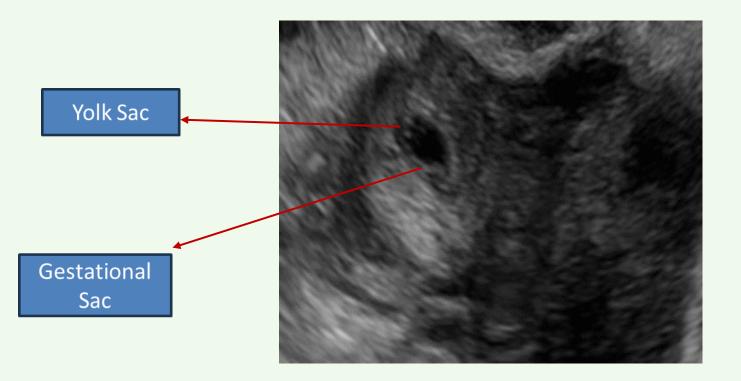








#### **Right adnexa**



#### Heterotopic





Defined as the presence of multiple gestations, with one being present in the uterine cavity and the other extrauterine, commonly in the fallopian tube and uncommonly in the cervix or ovary

Rare event in spontaneous conception 0.03 per 1000 pregnancies

ART incidence increases to 0.26 -1.5 per 1000 pregnancies (Krishnanmoorthy et al, 2021)







## Multiple Pregnancies and ART





Prior to 1984 nearly all viable embryos created through ovarian stimulation were transferred to optimise the chances of success leading to multiple pregnancies

1984 - The evolution of frozen embryo transfer led to a reduction in the transfer of > 3 embryos, but the transfer 2 - 3 embryos continued

2000 - The European Society of Human Reproduction and Embryology declared that a twin rate of > /= 25% is unacceptable

This led to the updating of legislation in some countries to impose an Elective single embryo transfer

Wyns et al. (2020)



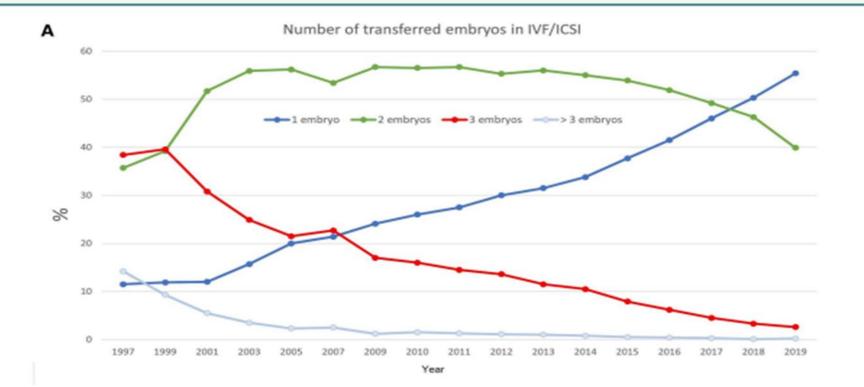


If the global incidence for post-IVF/ICSI twinning is assumed to be 25% and for Higher Order Multiple pregnancies to be 3%, these ~100 000 ongoing pregnancies will result in 72 000 singletons, 50 000 twin children and 9000 triplet children for a total of 131 000 children (Gerris et al, 2004)

Assuming an incidence of 10% for severe complications and sequelae per child born to a multiple pregnancy – IVF/ICSI is responsible for approximately 6,000 severely disabled children each year (Wennerholm and Gerris, 2000) **ESHRE 2020** 













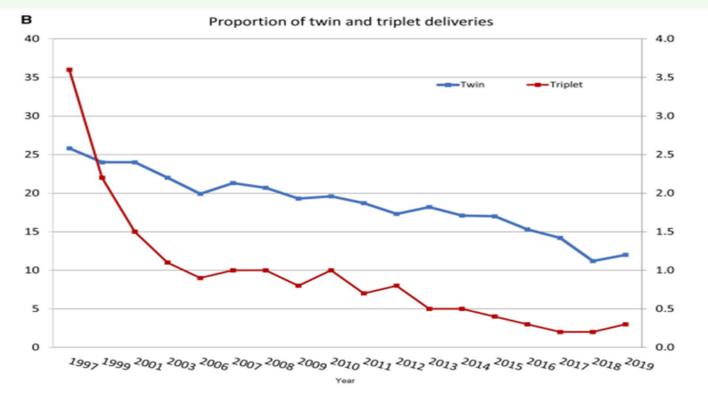


Figure 4. Embryo transfer and multiple births in Europe, 1997–2019. (A) Number of embryos transferred in IVF and ICSI during fresh cycles. (B) Percentages of twin and triplet deliveries.

Table 4. Number of embryos transferred after ART and deliveries in 2019.

		IVF + ICSI							FET		
Country	Transfers	1 embryo (%)	2 embryos (%)	3 embryos (%)	4+ embryos (%)	Deliveries	Twin (%)	Triplet (%)	Deliveries	<b>Twin (%)</b>	Triplet (%)
Albania	66	1.5	98.5	0.0	0.0	26	26.9	3.8	15	20.0	0.0
Armenia	544	26.1	52.4	21.5	0.0	211	16.1	3.3	702	3.6	0.6
Austria	5714	73.3	26.6	0.1	0.0	1640			961		
Belarus	2135	32.9	59.2	7.9	0.0	449	12.2	0.9	320	17.5	0.0
Belgium	12 048	72.5	24.5	2.7	0.3	2604	5.7	0.1	2902	4.2	0.0
Bosnia-Herzegovina,	71	76.1	19.7	4.2	0.0	26	3.8	0.0	11	18.2	0.0
Federation part											
Bulgaria											
Czech Republic	10 151	79.9	19.9	0.2	0.0	2033	5.7	0.1	3057	6.3	0.1
Denmark	8492	83.1	16.5	0.4	0.0	1695	3.5	0.1	1830	1.7	0.0
Estonia	1500	57.6	40.3	2.1	0.0	389	9.8	0.3	255	10.6	0.4
Finland	2564	95.7	4.3	0.0	0.0	680			892		
France	40 432	60.8	36.6	2.4	0.1	10 182	8.9	0.1	9613	5.4	0.1
Germany	53 737	34.4	62.6	3.0	0.0	12 936	18.1	0.4	6163	13.0	0.5
Greece	7284	23.5	61.0	13.2	2.2	1741	20.0	0.2	1584	17.3	0.3
Hungary	6883					1354	16.8	0.8	296	13.2	1.0
Iceland	299	100.0	0.0	0.0	0.0	82	0.0	0.0	125	2.4	0.0
Ireland	977	50.7	46.9	2.5	0.0	324	11.1	0.0	262	0.4	0.0
Italy	28 731	44.8	46.7	7.8	0.7	5151	12.3	0.3	4412	5.0	0.1
Kazakhstan	4193	51.9	46.5	1.6	0.0	1414	12.6	0.3	1702	12.0	0.1
Latvia	380	83.4	16.6	0.0	0.0	122	5.9	0.0	202	6.8	0.0
Lithuania	1386	56.1	29.5	14.4	0.0	256	11.0	1.7	28	29.2	0.0
Luxembourg	499	55.7	44.3	0.0	0.0	115	4.3	0.9	125	6.4	0.0
Malta	18					5			7		
Moldova											
Montenegro	481	29.7	49.1	21.2	0.0	148	23.6	0.0	29	20.7	0.0
North Macedonia	1734	35.9	62.2	1.8	0.1	488	14.8	0.0	81	11.1	0.0
Norway											
Poland	8884	66.9	32.9	0.1	0.0	2137	6.1	0.1	3400	4.1	0.1
Portugal	3692	54.0	45.6	0.4	0.0	941	9.9	0.2	801	9.0	0.1
Russia	58 120	61.1	38.5	0.3	0.0	13 758	12.5	0.2	13 737	12.2	0.2
Serbia	1511	23.5	31.8	41.8	3.0	380	28.7	1.6	71	9.9	0.0
Slovakia	0570	<b>64 0</b>	22.4			606	7.0		450	6.0	
Slovenia	2578	61.8 52.8	38.1	0.1	0.0	686	7.3	0.0	459	6.3	0.0
Spain	23 132		46.2	1.0		6020	11.0	0.1	8056	8.9	0.0
Sweden	8587	88.8 72.2	11.2	0.0	0.0	808	7.7	0.0	2668	1.8	0.0
Switzerland	3207	12.2	26.5	1.2	0.1	808	1.1	0.4	12/2	4.7	0.2
The Netherlands	7700	<b>FO 7</b>	41.2	0.0	0.0	2200	11.0	0.1	2204	12.4	0.0
Turkey	7796 5747	58.7	41.3 53.9	0.0	0.0	2388 2042	11.6 15.8	0.1	3294 5734	13.4 14.1	0.2
Ukraine		41.3		4.8	0.0	2042	15.8	0.2	5/34	14.1	0.0
UK All <sup>a</sup>	30 879 344 452	68.6 55.4	29.7 39.9	1.7 2.6	0.0	75 7 16	11.9	0.3	75.066	8.9	0.1
A11	344 452	>>.4	69.9	2.6	0.2	/5/16	11.9	0.3	/5 066	8.9	0.1

<sup>a</sup> Total refers only to these countries where data on number of transferred embryos and on multiplicity were reported. FET, frozen embryo transfer.

#### Irish Medical Journal 2012





Naasan et al, (2012) in their review of ART in Ireland summarised that the introduction of a state funded IVF programme with compulsory eSET should come sooner rather than later

## **Multiple Pregnancy**

Accurate assessment of chorionicity

Determination of chorionicity and amnionicity – best achieved before 14 weeks gestation

- Number of placental masses
- Lambda Sign
- T- sign

#### **Dichorionic Diamniotic Twin Pregnancy**









#### DCDA – LAMBDA SIGN





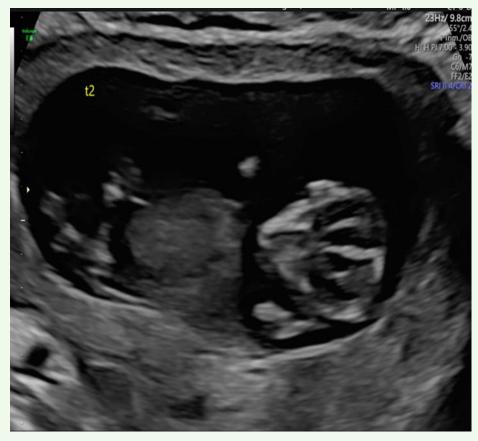


## Monochorionic Diamniotic Twin Pregnancy









#### Membrane







#### Dichorionic Tri-amniotic Triplet Pregnancy



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#### Tri-chorionic Tri-amniotic Triplet pregnancy







#### **Complications of Multiple Pregnancies**





<u>Maternal</u> Pregnancy Induced Hypertension Pre-Eclampsia Pre-term labour

#### <u>Fetal</u>

Premature delivery Twin to twin transfusion Fetal Growth Restriction Increase in perinatal morbidity and mortality Post ART treatment presentation to hospital





Consider differential diagnosis:

Haemorrhage - vaginal or intra-abdominal

Infection

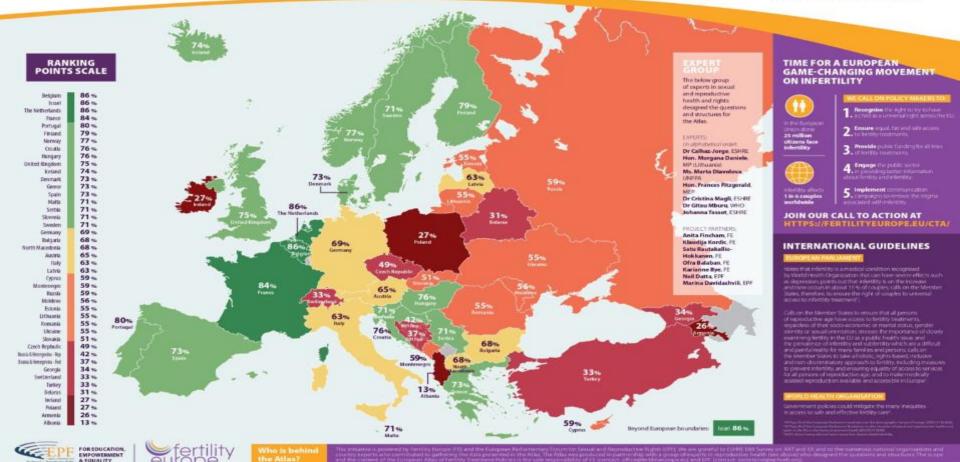
OHSS – primary / secondary

**Ovarian Torsion** 

Complications of early pregnancy

## EUROPEAN ATLAS OF FERTILITY TREATMENT POLICIES

DECEMBER 2021



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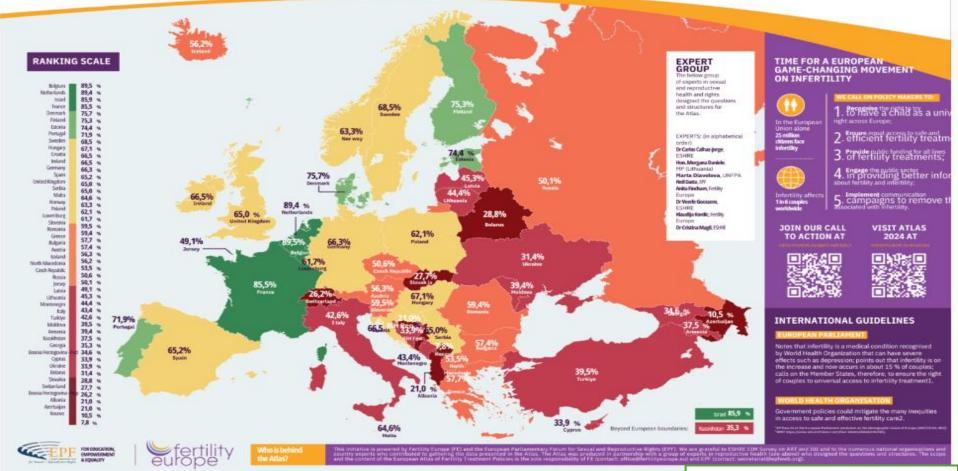
## Key Findings (2021) - Overall

Out of 43 countries analysed

Excellent (100-81%)	Very good (80-70%)	<b>Medium</b> (69-60%	<b>Poor</b> (59-50%)	<b>Very poor</b> (49-31%)	Exceptionally Poor (30-0%)
Good regulations. Access to treatments for most patients. Good funding.	Quite good regulations. Access to treatments to many groups of patients. Quite good funding.	Access to treatment for selected groups. Variable funding.	Access to treatments for selected groups. Poor funding.	Access to treatments limited. Funding poor or none.	Access to treatments very limited. No funding.
Belgium 86 France 84 Israel 86 The Netherlands 86	Croatia 76 Denmark 73 Finland 79 Greece 73 Hungary 76 Iceland 74 Malta 71 Norway 77 Portugal 80 Serbia 71 Slovenia 71 Slovenia 71 Spain 73 Sweden 71 United Kingdom 75	Austria 65 Bulgaria 68 Germany 69 Italy 63 Latvia 63 North Macedonia 68	Cyprus 59 Estonia 55 Lithuania 55 Moldova 56 Montenegro 59 Romania 56 Russia 59 Slovakia 51 Ukraine 55	Belarus 31 Bosnia & Herzegovina (37, 42) Czech 49 Georgia 34 Switzerland 33 Turkey 33	Albania 13 Armenia 26 Ireland 27 Poland 27

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#### EUROPEAN ATLAS OF FERTILITY TREATMENT POLICIES For more information, please visit epfweb.org



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# Thank you

# Questions?