CLINICAL CENTRE OF VOJVODINA
DEPARTMENT FOR OB. AND GYN.

RISKS OF IVF MULTIPLE PREGNANCIES - OUR EXPERIENCE

Prof.dr Vesna Kopitović

In vitro fertilization – the beginining

- 25.07.1978. Louisa Brown
- Patric Steptoe and Robert Edwards
- Age of assisted reproductive technology(ART) started
- The era of hope for many couples
- Hope, joy and success but also many new challenges

Original letters to the Editor of Lancet

Letters to the Editor

BIRTH AFTER THE REIMPLANTATION OF A HUMAN EMBRYO

SIR, — We wish to report that one of our patients, a 30-year-old nulliparous married women, was safely delivered by cæsarean section on July 25, 1978, of a normal infant girl weighing 2700 g. The patient had been referred to one of us (P.C.S) in 1976 with a history of 9 years' infertility, tubal occlusions, and unsuccessful salpingostomies done in 1970 with excision of the ampullæ of both oviducs followed by persistent tubal blockages. Laparoscopy in February, 1977, revealed grossly distorted tubal remnants with occlusion and peritubal and ovarian adhesions. Laparotomy in August, 1977, was done with excision of the remains of both tubes, adhesolysis, and suspension of the ovaries in good position for oocyte recovery.

Pregnancy was established after laparoscopic recovery of an oocyte on Nov. 10, 1977, in-vitro fertilization and normal cleavage in culture media, and the reimplantation of the 8-cell embryo into the uterus $2^{1}/_{2}$ days later. Amniocentesis at 16 weeks' pregnancy revealed normal α-fetoprotein levels, with no chromosome abnormalities in a 46 XX fetus. On the day of delivery the mother was 38 weeks and 5 days by dates from her last menstrual period, and she had pre-eclamptic toxæmia. Blood-pressure was fluctuating around 140/95, œdema involved both legs up to knee level together with the abdomen, back, hands, and face; the blood-uric-acid was 390 µmol/l, and albumin 0·5 g/l of urine. Ultrasonic scanning and radiographic appearances showed that the fetus had grown slowly for several weeks from week 30. Blood-œstriols and human placental lactogen levels also dropped below the normal levels during this period. However, the fetus grew considerable during the last 10 days before delivery while placental function improved greatly. On the day of delivery the biparietal diameter had reached 9·6 cm, and 5 ml of amniotic fluid was removed safely under sonic control. The lecithin: sphingomyelin ratio was 3·9:1, indicative of maturity and low risk of the respiratory-distress syndrome.

We hope to publish further medical and scientific details in your columns at a later date.

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University Physiology Laboratory,
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R. G. EDWARDS

IVF - Challenges

- Success, practical technical challenges
- Clinical challenges in the field of reproductive medicine and perinatology
- Legal, legislative dilemma
- Ethical, moral and religious dilemmas
- Organizational dilemmas
- Complications !!!

The key dilemma - BALANCE

MULTIPLE PREGNANCIES AND IN VITRO FERTILIZATION

- The desire for greater success occurrence of multiple embryo transfer
- The high rate of multiple pregnancies
- ARE MULTIPLE PREGNANCIES SUCCESS OR COMPLICATIONS OF IN VITRO FERTILIZATION?
- Will mode of conception further affect this phenomenon?

Multiple pregnancies - facts

- After natural conception, the chance of a multiple pregnancy is between 1 and 2% (spontaneous multiple pregnancy).
- After ICSI/IVF currently in Europe around 20 % of pregnancies are multiple (19.4% twins and 0.8% triplets)(Farraretti et al. Human Reproduction, 2013), and 30% USA.
- In 2005 1% of infants born in US were ART, and accounted of 17% of multiple births (Wright et al. 2008)
- 80% of twins are dizygotic and 20% are monozygotic.
- IVF/ICSI lead to increased incidence in monozygotic twining.
- Total multiple delivery rate of 20.2% in 2009, compared with 21.7% in 2008, 22.3% in 2007, 20.8% in 2006 and 21.8 % in 2005 shows slow but stabile decline (Farraretti et al. Human Reproduction, 2013).

Multiple pregnancies - facts

- Dramattical increase in last few decades due to introduction of MAR.
- Between 1970 and 2003, twinning increased by 50% and triplets by 400% in England and Wales,1 mirroring similar trends in the USA.

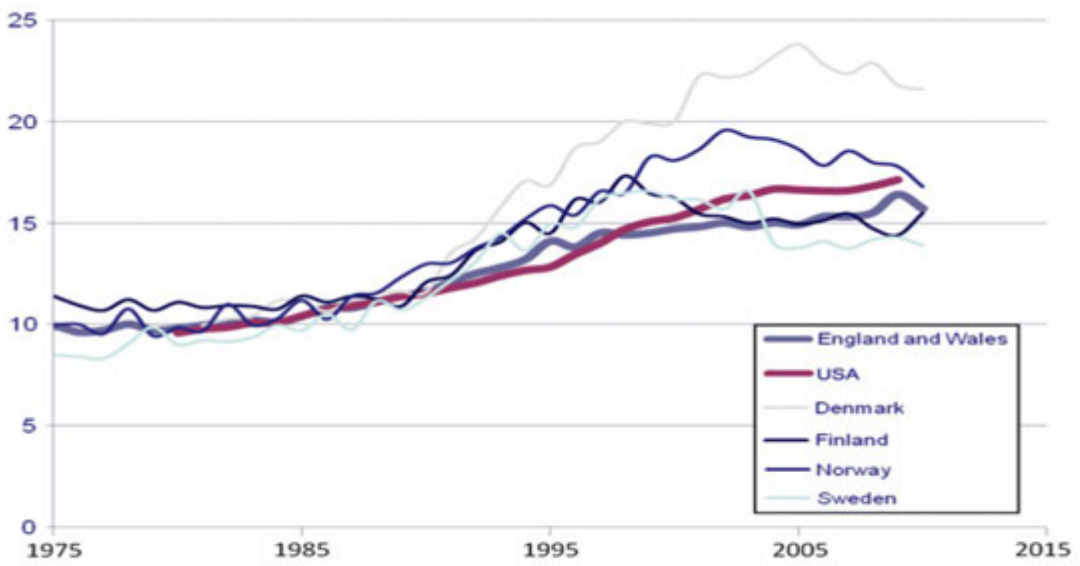
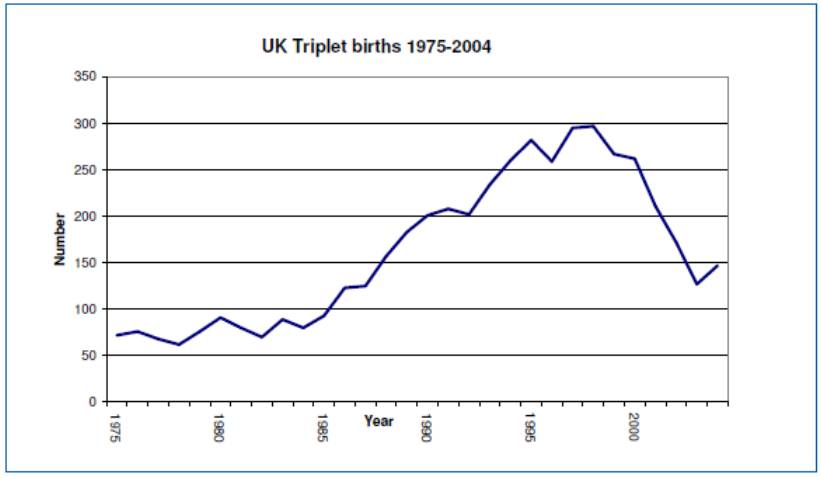
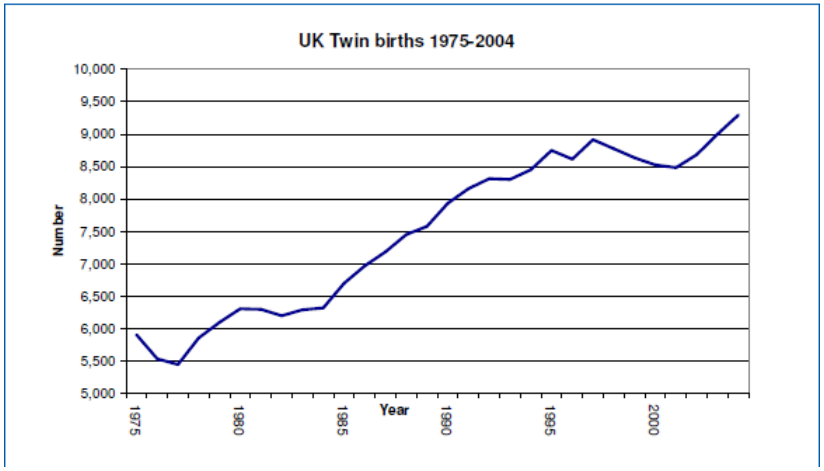
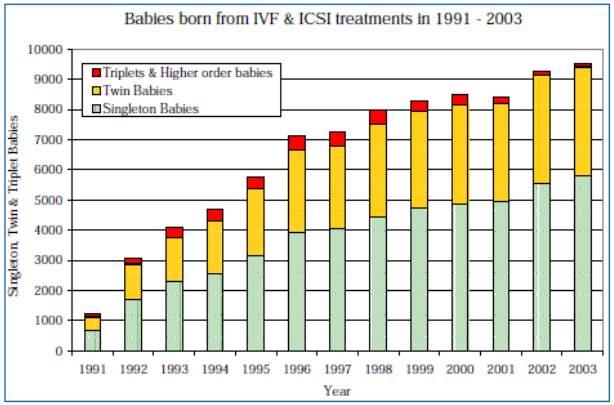


Fig. 1. The proportion of multiple births in six countries (per 1000 births). Published with permission.[4]

Multiple pregnancies - facts





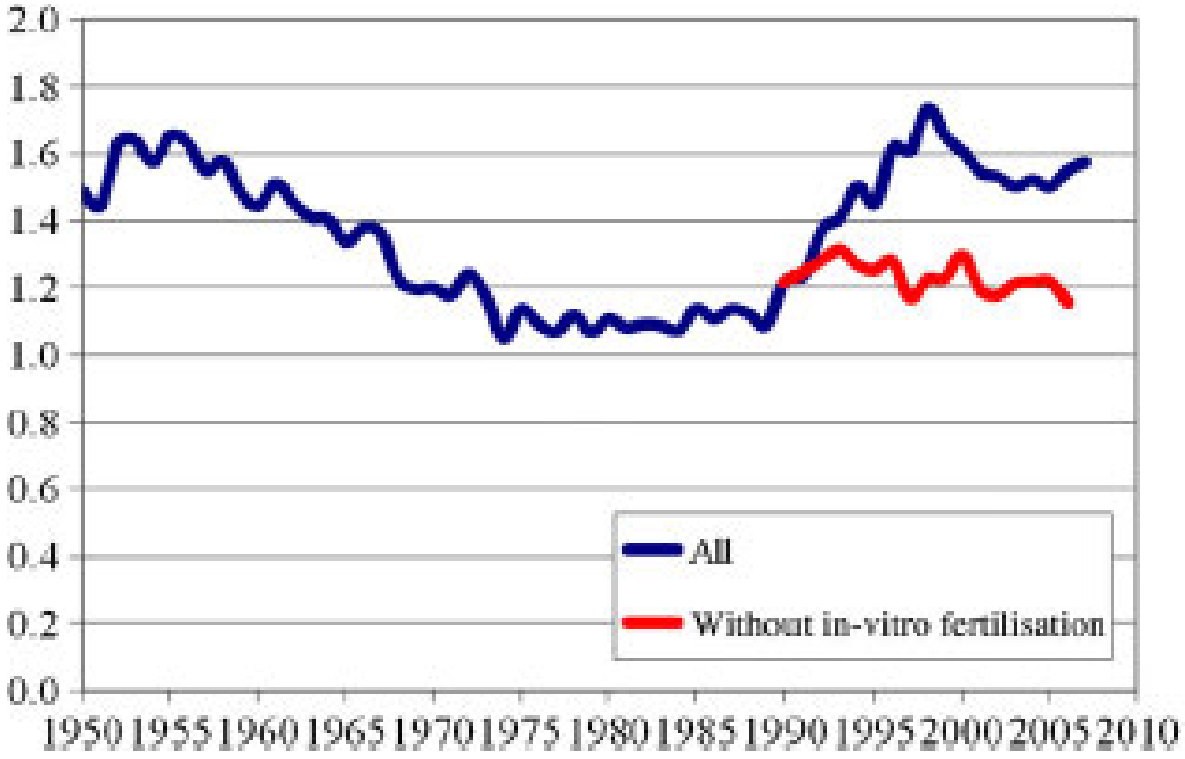


Number of singleton, twins and triplet born following IVF/ICSI procedures in the UK (HFEA register data)

Risks for the occurrence of multiple pregnancies

- ART
- Induction of ovulation
- Mothers age (37 years, the best chance for twins)
- Latitude (closer to the equator)
- Nutrition, endogamy, parity, BMI
- Hereditary predisposition
- Higher FSH

ART AND MULTIPLE PREGNANCY
Tiitinen et al.



Best Pract Res Clin Obstet Gynaecol. 2012, Tiitinen A.

Infertility and assisted reproductive technology

- The term infertility is defined as inability of achieving pregnancy after one year of sexual intercourse without using contraception methods (Speroff).
- Incidence in the world is 10-15%
- 56% of couples seek treatment.
- 16-18% of couples in our community.

- The initial success of 0.5-1%, today is about 30% and in some centers more than 50%.

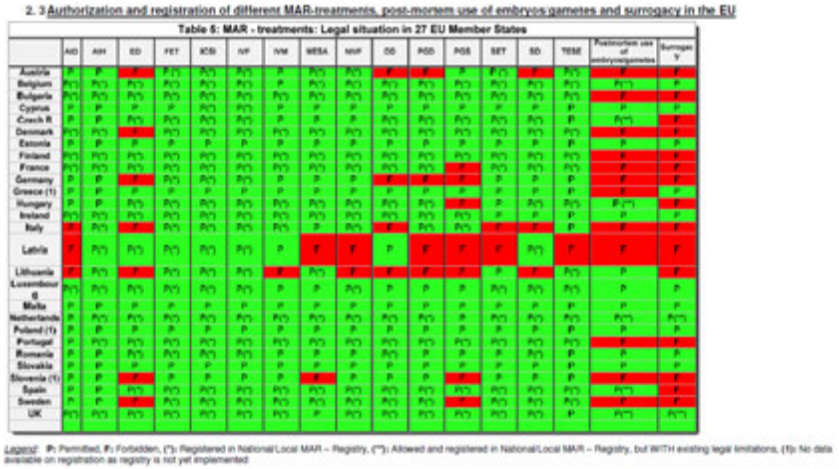
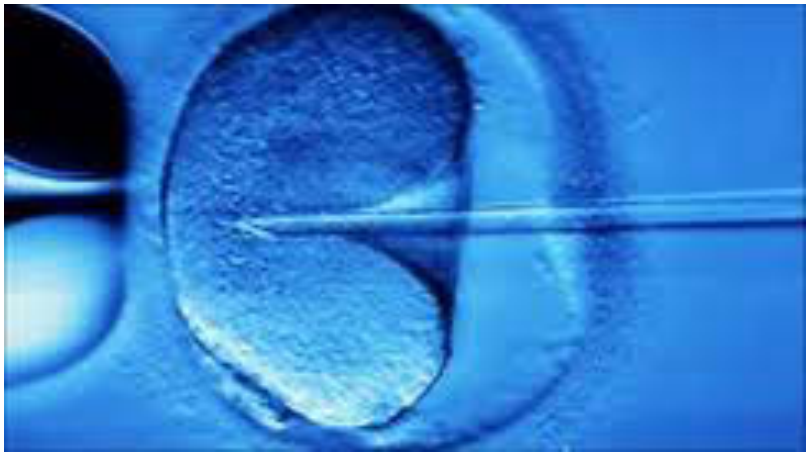

2. 3 Authorization and registration of different MAR-treatments, post-mortem use of embryos gametes and surrogacy in the EU

Table 5: MAR - treatments: Legal situation in 27 EU Member States

Expansive development of procedures, controls and legislation sometimes lags - a consequence of complications

IVF/ICSI = ART = MAR (Medically Assisted Reproduction) – Facts - SCOPE

- More than 5 million babies born
- In 2009. Europe 537 463 cycles
- MAR children (0,6%-4.5% of all children)
- 19.4% twins (5.9%-36.4%)
- 0.8% triplets (0%-6.7%)



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human reproduction ORIGINAL ARTICLE *ESHRE pages*

Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE†

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STUDY QUESTION: The 13th European in vitro fertilization (IVF)-monitoring (EIM) report presents the results of treatments involving assisted reproductive technology (ART) initiated in Europe during 2009: are there any changes in the trends compared with previous years?

SUMMARY ANSWER: Despite some fluctuations in the number of countries reporting data, the overall number of ART cycles has continued to increase year by year and, while pregnancy rates in 2009 remained similar to those reported in 2008, the number of transfers with multiple embryos (3+) and the multiple delivery rates declined.

WHAT IS KNOWN ALREADY: Since 1997, ART data in Europe have been collected and reported in 12 manuscripts, published in Human Reproduction.

STUDY DESIGN, SIZE, DURATION: Retrospective data collection of European ART data by the EIM Consortium for the European Society of Human Reproduction and Embryology (ESHRE); cycles started between 1st January and 31st December are collected on a yearly basis; the data are collected by the National Registers, when existing, or on a voluntary basis.

PARTICIPANTS/MATERIALS SETTING, METHODS: From 34 countries (+2 compared with 2008), 1005 clinics reported 537 463 treatment cycles including IVF (135 621), intracytoplasmic sperm injection (ICSI, 266 084), frozen-embryo replacement (FER, 104 153), egg donation (ED, 21 604), in vitro maturation (IVM, 1334), preimplantation genetic diagnosis/screening (PGD/PGS, 4389) and frozen oocyte replacements (FOR, 4278). European data on intrauterine insemination using husband/partner's semen (IUI-H) and donor (IUI-D) semen were reported from 21 and 18 countries, respectively. A total of 162 843 IUI-H (+12.7%) and 29 235 IUI-D (+17.3%) cycles were included. Data available from each country are presented in the tables; total values (as numbers and percentages) refer to those countries where all data have been reported.

MAIN RESULTS AND THE ROLE OF CHANCE: In 21 countries where all clinics reported to the ART register, a total of 399 020 ART cycles were performed in a population of 373.8 million, corresponding to 1067 cycles per million inhabitants. For IVF, the clinical pregnancy rates per aspiration and per transfer were 28.9 and 32.9%, respectively and for ICSI, the corresponding rates were 28.7 and 32.0%. In FER cycles, the pregnancy rate per thawing was 20.9%, in ED cycles, the pregnancy rate per transfer was 42.3%. The delivery rate after IUI-H was 8.3 and 13.4% after IUI-D. In IVF and ICSI cycles, 1, 2, 3 and 4+ embryos were transferred in 24.2, 57.7, 16.9 and 1.2%, respectively. The proportions of singleton, twin and triplet deliveries after IVF and ICSI (combined) were 79.8, 19.4 and 0.8%, respectively, resulting in a total multiple delivery rate of 20.2%, compared with 21.7% in 2008, 22.3% in 2007, 20.8% in 2006 and 21.8% in 2005. In FER cycles, the multiple delivery rate was 13.0% (12.7% twin and 0.3% triplets). Twin and triplet delivery rates associated with IUI cycles were 10.4/0.7% and 10.3/0.5%, following treatment with husband and donor semen, respectively.

LIMITATIONS, REASONS FOR CAUTION: The method of reporting varies among countries, and registers from a number of countries have been unable to provide some of the relevant data such as initiated cycles and deliveries. As long as data are incomplete and generated through different methods of collection, results should be interpreted with caution.

†ESHRE pages content is not externally peer reviewed. The manuscript has been approved by the Executive Committee of ESHRE.

‡EIM Committee 2011–2013: chairman: A.P.F.; chairman-elect: M.K.; past chairman: J.A.M.; members: A.N.A. (special advisor), S.B., J.A.C., V.K. and K.E. V.G. is a science manager at ESHRE Central Office, Brussels. See also Appendix for contributing centres and contact persons representing the data collection programmes in the participating European countries.

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Table III Number of embryos transferred and deliveries after ART in 2009.

Country	IVF + ICSI								FER		
	Transfers	1 embryo (%)	2 embryos (%)	3 embryos (%)	4+ embryos (%)	Deliveries	Twin (%)	Triplet (%)	Deliveries	Twin (%)	Triplet (%)
Austria	5875	22.5	68.2	8.6	0.7	1039	21.8	0.8			
Belgium	16 089	48.9	40.7	8.6	1.8	3275	10.3	0.2	1020	11.0	0.2
Bulgaria	1443	9.1	32.3	47.5	10.9	415	12.5	2.7	14	14.3	14.3
Croatia	2774					586	18.4	2.7			
Cyprus						411					
Czech Republic	10 146	19.9	72.8	7.2	0.1						
Denmark	9664	42.0	52.1	6.0	0.0	2056	16.0	0.0	334	17.1	0.0
Finland	3981	65.7	34.1	0.2	0.0	998	8.4	0.1	586	9.2	0.0
France	47 822	27.1	61.8	10.3	0.8	11 292	18.0	0.3	2287	9.9	0.3
Germany	45 476	13.3	68.1	18.7		6717	20.1	0.8	1643	14.9	0.5
Greece	1481	21.7	31.0	40.9	6.4	219	27.6	2.8	23	28.6	9.5
Hungary	5693	14.5	55.7	27.2	2.6						
Iceland	389	43.2	56.8	0.0	0.0	89	14.6	0.0	43	9.3	0.0
Ireland	2487	25.7	65.9	8.3	0.0	627	21.9	1.0	114	8.0	0.0
Italy	37 301	19.0	33.6	44.8	2.6	6409	21.1	2.4	113	12.4	0.0
Kazakhstan	886	13.9	43.5	39.1	3.6	236	36.4	1.7	54	18.5	0.0
Latvia	440	23.0	63.9	13.2	0.0						
Lithuania	114	9.6	13.2	36.0	41.2	30	33.3	6.7	2	0.0	0.0
Macedonia	1703	14.9	29.5	55.6	0.0	584	32.2	1.9	13	7.7	0.0
Moldova	554	8.7	25.1	54.5	11.7	208	21.2	1.4			
Montenegro	398	16.3	29.1	49.5	5.0	137	20.4	1.5	6	16.7	0.0
Norway	5451	53.4	45.7	0.9	0.0	1450	11.6	0.1	357	7.9	0.3
Poland	6884	20.7	67.4	11.3	0.6	1866	16.9	0.8	485	15.9	0.0
Portugal	3877	20.6	71.2	7.9	0.3	1006	22.1	0.9	124	15.3	0.8
Romania	875	14.1	39.9	34.3	11.8	46	28.3	4.3	1	0.0	0.0
Russia	29 208	16.4	60.5	19.4	3.6	6308	25.6	1.3	655	15.5	0.6
Serbia	1092	15.7	20.7	42.4	21.2	329	31.0	6.4			
Slovenia	2513	30.4	66.9	2.6	0.0	734	17.6	0.1	100	9.0	0.0
Spain	26 583	15.6	68.2	16.1	0.0	5858	23.3	0.6	1038	17.9	0.5
Sweden	9614	70.7	29.3	0.0	0.0	2580	5.9	0.2	962	5.3	0.0
Switzerland	4170	16.9	64.9	18.2	0.0	903	19.7	0.1	531	13.7	0.2
The Netherlands	13 888					3503	11.2	0.1	883	7.9	0.3
Ukraine	5334	10.6	50.4	35.2	3.7	1667	24.4	1.9	278	21.9	0.4
United Kingdom	36 591	22.7	72.1	5.3	0.0	10 749	22.4	0.4	1703	17.1	0.1
All*	340 799	24.2	57.7	16.9	1.2	72 327	19.4	0.8	13369	12.7	0.3

ART, assisted reproductive technology; FER, frozen embryo replacement; ICSI, intracytoplasmic sperm injection.
*Totals refer only to those countries where data on the number of transferred embryos and on multiplicity were reported.

Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE

Table V. *Number of embryos transferred after IVF and ICSI in 2004.*

Country	All transfers	1 embryo	%	2 embryos	%	3 embryos	%	4+ embryos	%
Albania	102	10	9.8	22	21.6	22	21.6	48	47.1
Austria	4315	632	14.6	2743	63.6	878	20.3	62	1.4
Belgium	12 787	6247	48.9	5379	42.1	972	7.6	189	1.5
Bulgaria	855	64	7.5	240	28.1	419	49.0	132	15.4
Denmark	7795	2134	27.4	5259	67.5	402	5.2	0	0.0
Finland	4176	1953	46.8	2191	52.5	11	0.3	0	0.0
France	43 821	7689	17.5	25 917	59.1	8176	18.7	2039	4.7
Germany	35 951	4176	11.6	22 029	61.3	9746	27.1	0	0.0
Greece	6953	1005	14.5	1640	23.6	2788	40.1	1520	21.9
Hungary	2334	175	7.5	651	27.9	1055	45.2	453	19.4
Iceland	199	42	21.1	132	66.3	25	12.6	0	0.0
Ireland (Rep.)	1705	134	7.9	1330	78.0	218	12.8	23	1.3
Italy	18 521	3382	18.3	5989	32.3	8983	48.5	167	0.9
Latvia	120	23	19.2	64	53.3	33	27.5	0	0.0
Lithuania	76	9	11.8	13	17.1	38	50.0	16	21.1
Macedonia	407	86	21.1	124	30.5	151	37.1	46	11.3
Norway	4554	1161	25.5	3377	74.2	16	0.4	0	0.0
Poland	3344	433	12.9	2170	64.9	661	19.8	80	2.4
Portugal	2257	335	14.9	1272	56.5	600	26.7	43	1.9
Russia C.I.S.	10 904	1436	13.2	5194	47.6	3049	28.0	1214	11.1
Serbia and Montenegro	126	29	23.0	18	14.3	32	25.4	47	37.3
Slovenia	1787	474	26.5	1090	61.0	223	12.5	0	0.0
Spain	21 085	2798	13.3	10 500	49.8	7787	36.9	0	0.0
Sweden	8135	5486	67.4	2642	32.5	7	0.1	0	0.0
Switzerland	2752	344	12.5	1782	64.8	525	19.1	3	0.1
The Netherlands*	12 474								
Turkey	3015	277	9.2	551	18.3	1185	39.3	1002	33.2
Ukraine	1339	233	17.4	283	21.1	396	29.6	427	31.9
UK	26 092	2452	9.4	22 195	85.1	1445	5.5	0	0.0
All	225507	43 219	19.2	124797	55.3	49 843	22.1	7511	3.3

Data restricted to those transfers where the number of embryos transferred is known. Finland: no data available for 16 IVF cycles and 5 ICSI cycles. Portugal: no data available for 7 ICSI cycles. Russia: no data available for 7 IVF cycles and 4 ICSI cycles. Switzerland: no data available for 5 IVF cycles and 93 ICSI cycles.
*Total excludes transfers from The Netherlands and Norway as the number of embryos transferred is not known for these countries.

Table X. *Singleton, twin, triplet and quadruplet deliveries after IVF and ICSI in 2004.*

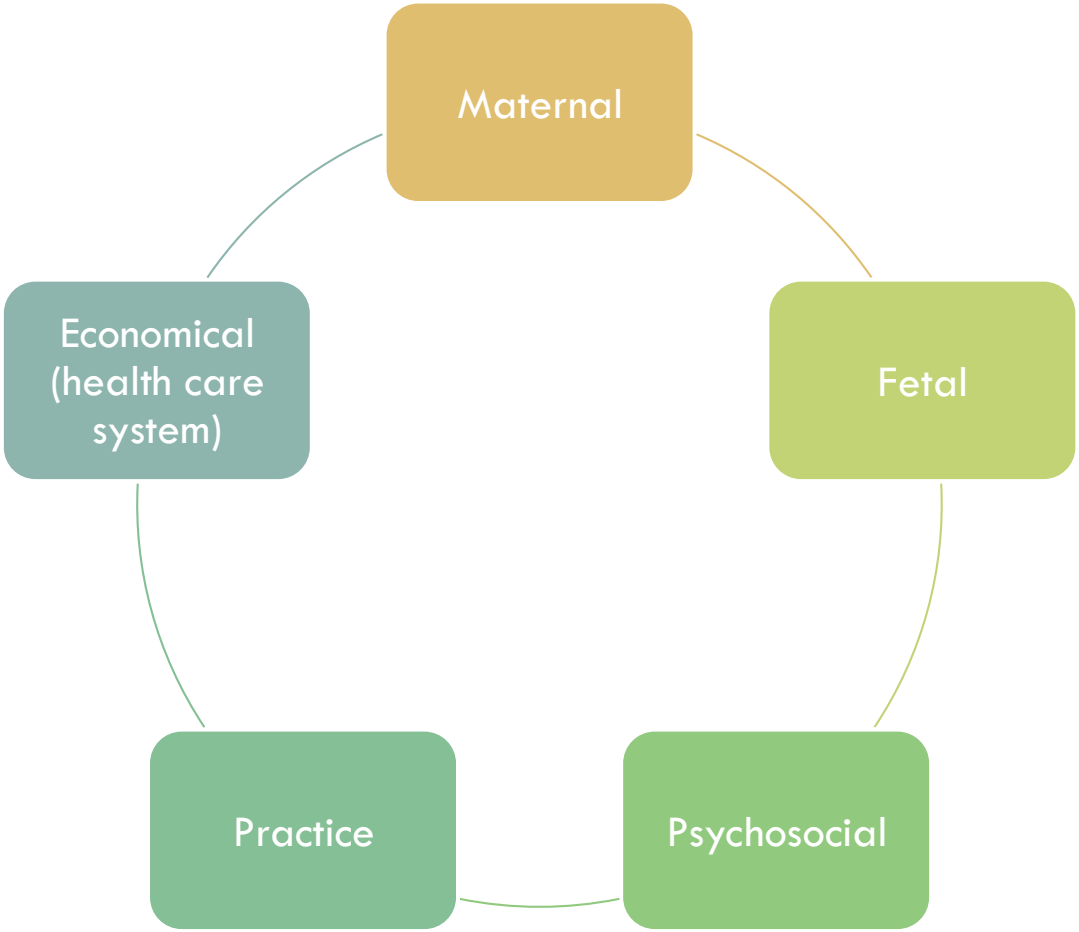
Country	All deliveries	Clinical pregnancies	Documented pregnancy loss	Lost to follow-up	Singleton deliveries	%	Twin deliveries	%	Triplet deliveries	%
Albania	10	25	15	0	7	70.0	3	30.0	0	0.0
Austria	233	1349			165	70.8	65	27.9	3	1.3
Belgium	1802	2814			1614	89.6	184	10.2	4	0.2
Bulgaria	210	256	36	9	149	71.0	54	25.7	7	3.3
Denmark	1980	2563	338	245	1557	78.6	416	21.0	7	0.4
Finland	886	1133	245	2	768	86.7	114	12.9	4	0.5
France*	8961	11 696	2735	36*	6911	77.1	1966	21.9	48	0.5
Germany	6699	10 252	2422	1131	5239	78.2	1386	20.7	74	1.1
Greece	1234	2526	280	1012	837	67.8	378	30.6	19	1.5
Hungary	604	795	160	31	386	63.9	199	32.9	19	3.1
Iceland	53	63	10	0	41	77.4	10	18.9	2	3.8
Ireland (Rep.)	393	509	110	5	302	76.8	89	22.6	2	0.5
Italy	3006	4826	945	875	2305	76.7	640	21.3	61	2.0
Latvia	22	34	7	5	16	72.7	6	27.3	0	0.0
Lithuania	10	21	6	5	6	60.0	3	30.0	1	10.0
Macedonia	59	84	24	1	42	71.2	15	25.4	2	3.4
Norway	1100	1358	246	25	828	75.3	255	23.2	3	0.3
Poland	842	1187	142	203	650	77.2	181	21.5	11	1.3
Portugal	477	651	142	32	358	75.1	113	23.7	6	1.3
Russia C.I.S.	2109	3698	603	986	1542	73.1	525	24.9	42	2.0
Serbia/Montenegro										
Slovenia	444	553	100	13	360	81.1	77	17.3	3	0.7
Spain	3818	7866	1283	2765	2790	73.1	959	25.1	69	1.8
Sweden	2027	2566	526		1912	94.3	114	5.6	1	0.0
Switzerland	528	732	155	49	410	77.7	112	21.2	6	1.1
The Netherlands										
Turkey	570	1337	166	602	346	60.7	207	36.3	17	3.0
Ukraine	304	375	69	2	193	63.5	106	34.9	5	1.6
UK	6747	7633	779	107	5112	75.8	1613	23.9	22	0.3
All	45 128	66 902			34 846	77.2	9[illegible]	21.7	438	1.0

A total of three quadruplet deliveries were recorded. These were not included in the table or in the total number of deliveries. Deliveries refer to those deliveries with documented number of infants. For Austria and Belgium, no numbers on pregnancy loss and loss for follow-up were reported. No data are available for Serbia and Montenegro and The Netherlands.
*France: for all 'lost to follow up' cases there was delivery, but no details could be reported.

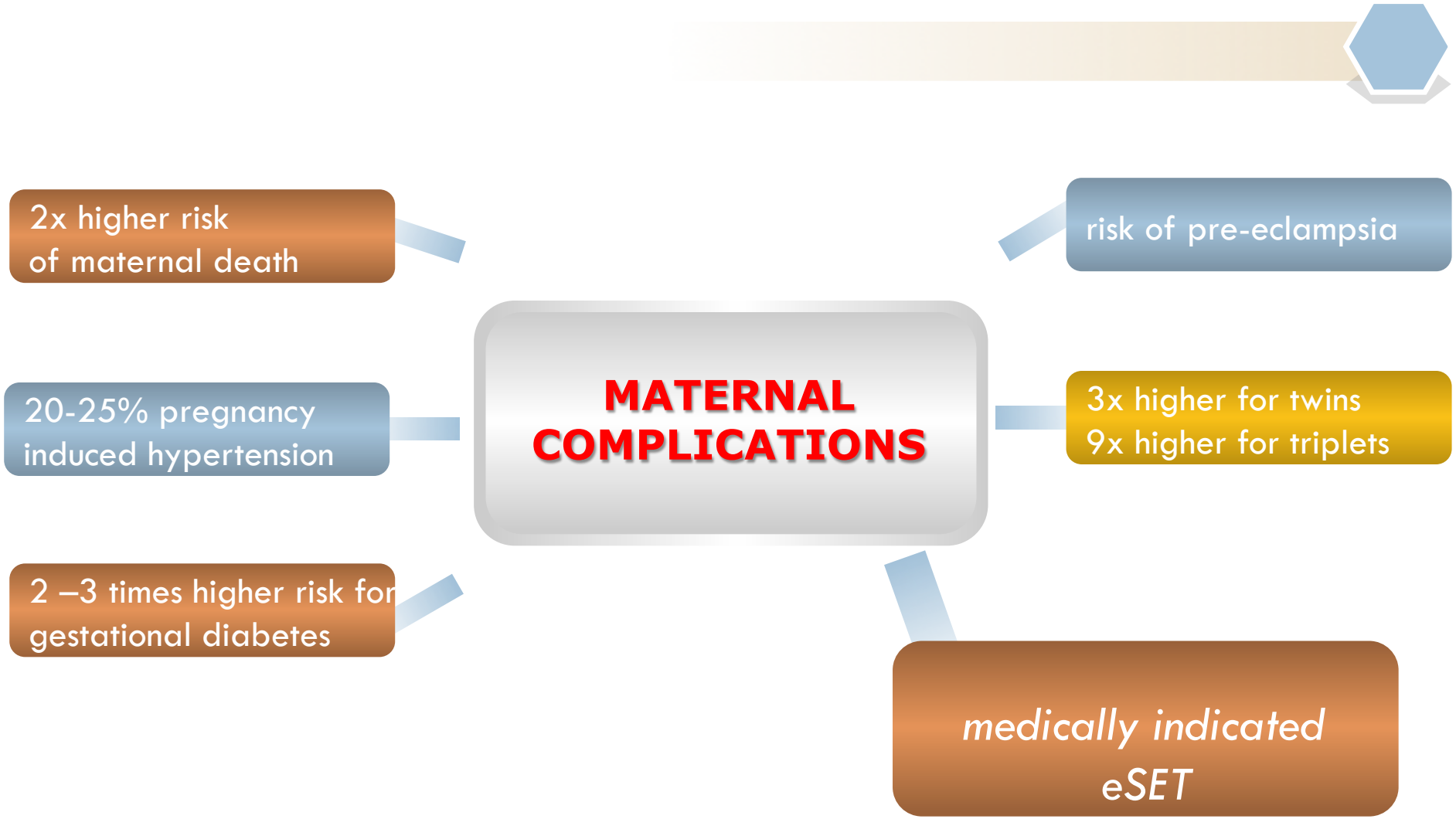
PROBLEM of multiple pregnancies Spontaneous and after ART

- Success itself is not the only goal
- Primum non noccere
- Only a healthy baby from a singleton pregnancy is a success in the proceedings IVF
- 2004. - BEST proposed concept

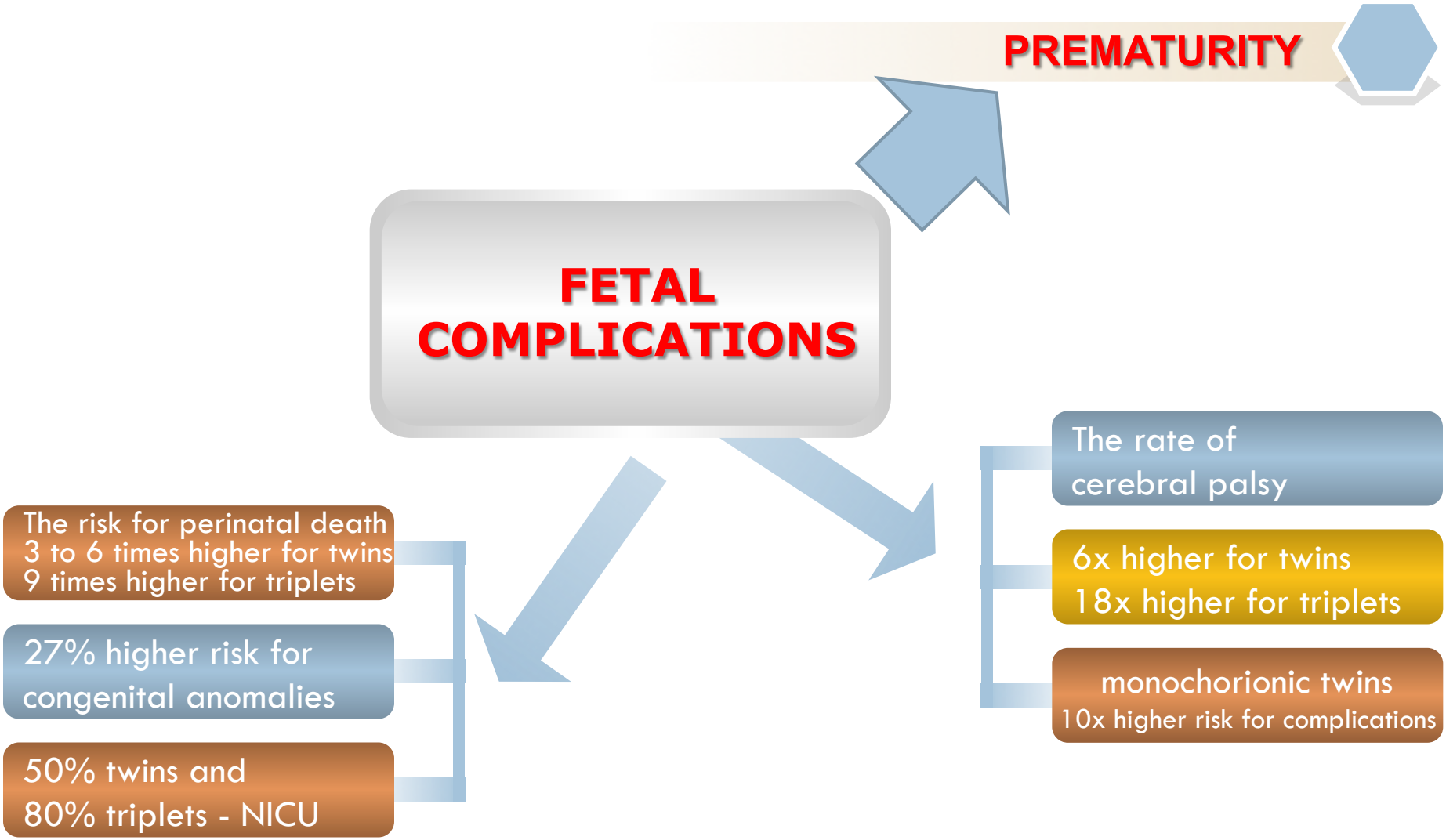
Risks of multiple pregnancies after IVF/ICSI



Risks for mothers



Risks for the fetus



Psychological and social consequences

Psychological and social consequences

Did you had a good sleep?

Have you seen this in a store?

Time to eat?

Psychological and social consequences

Do you need a new car?

Do you need a bigger house?

When did this parentes have last time good sleeping?

Do not be irresponsibile!

Economical (health care system) risks

Neonatal costs – twins 16 X
– triplets 109 X

A British study – triplets pregnancy - 2000 cycles

Posledice neadekvatnog reimbursmenta – Nemogućnost implementacije eSET i visoka stopa multiplih trudnoća

- Procenjeno je da jedna troplodna trudnoća košta zdravstveni sistem i do 2000 pokušaja VTO
- Implementacija eSET-a u najvećoj meri zavisi od dobre reimbursement politike.

One child at a time

Reducing multiple births after IVF

Report of the Expert Group on Multiple Births after IVF

Professor Peter Braude

- Doing 30% eSET cycles leads to a twin birth rate of around 20%;
- Doing 50% eSET cycles leads to a twin birth rate of around 10%;
- Doing 70% eSET cycles leads to a twin birth rate of around 5%.

after the babies themselves was even more striking: neonatal twin costs were 16 times high than singleton costs; triplet costs 109 times higher.[50] Neonatal and paediatric services in t

work differently from the UK: generally patients have better access to publicly funded IVF treatments, which directly influences patients' attitudes to eSET, and their patient profile

Practice risks -numerous dilemmas that arise in multiple gestation menagement from validity of diagnostic tools and perinatal and obstetrical protocols. Medico-legal issues?

Practice points

- Chorionicity assessment is important to improve screening performance in multiple pregnancies.
- Screening methods including an ultrasound component perform better then serum based only methods in multiple pregnancies and should be the standard of care.
- Non Invasive Prenatal Testing is promising in multiple pregnancies but there is currently only limited information on the performance of this test.
- Amniocentesis technique must be adapted to a multiple pregnancy. The risk of sampling the same sac twice is around 1–2% and should be discussed in advance.
- Chorionic villus sampling carries additional challenges in polychorionic multiple pregnancies. Sampling technique must be modified accordingly. The risk of sampling the same placenta twice is around 2–4% and should be discussed in advance.
- Chorionic Villous Sampling and Amniocentesis seem to carry a similar rate of procedure related loss in multiple pregnancies.

Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 285–294

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journal homepage: www.elsevier.com/locate/bpobgyn

9

Prenatal screening and diagnosis of aneuploidy in multiple pregnancies

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Keywords:
prenatal screening
Down syndrome
aneuploidy
multiple pregnancies
amniocentesis
chorionic villus sampling

Prenatal screening for aneuploidy has changed significantly over the last 30 years, from being age-based to maternal serum and ultrasound based techniques. Multiple pregnancies present particular challenges with regards to screening as serum-based screening techniques are influenced by all feti while ultrasound-based techniques can be fetus specific. Tests currently available tend to not perform as well in multiple compared to singleton pregnancies. Considerations must be given to these variations when discussing and performing screening for aneuploidy in this situation. Prenatal invasive diagnosis techniques in multiple pregnancies bring their own challenges from a technical and counselling point of view, in particular with regards to sampling error, mapping and assignment of results and management of abnormal results. This review addresses these particular challenges and provides information to facilitate care.

Are all those risks consequence of MAR or multiple pregnancies per se

Table 3 Neonatal outcomes in the two groups.

Variable	IVF group (N = 290)	SC group (N = 350)	P value
GA at delivery (wks)	34.9 ± 2.6	34.7 ± 3.1	0.375
Gender			
Like-sex (%)	140 (48.3%)	170 (48.6%)	
Unlike-sex (%)	150 (51.7%)	180 (51.4%)	0.941
Mean birth weight (g)	2235 ± 557	2196 ± 576	0.208
LBW	45 (15.5%)	54 (15.4%)	0.975
VLBW	40 (13.7%)	47 (13.4%)	0.893
SGA	24 (8.2%)	28 (8%)	0.899
Birth weight discordance	25 (8.6%)	26 (7.4%)	0.579
Low Apgar score at 5 m	28 (9.7%)	30 (8.6%)	0.634
NICU admission	70 (24.1%)	80 (22.6%)	0.703
Congenital anomalies	14 (4.8%)	15 (4.3%)	0.743
Pulmonary morbidity	7 (2.4%)	8 (2.3%)	0.915
Cerebral morbidity	8 (2.8%)	9 (2.6%)	0.883
Perinatal Mortality	3 (1%)	3 (0.9%)	0.817

N: number, IVF: in vitro fertilization, SC: spontaneous conception, P: probability, SGA: small for gestational age, LBW: low birth weight, NICU: neonatal intensive care unit.

Middle East Fertility Society Journal (2012) 17, 231–235

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefjournal.org
www.sciencedirect.com

ORIGINAL ARTICLE

Obstetric and neonatal outcomes of IVF versus spontaneously conceived dichorionic twins

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Available online 11 August 2012

Table 2 Obstetric complications in the two groups.

Variable	IVF group (N = 145)	SC group (N = 175)	P value
Gestational duration (wks)			
24–28	19 (13.2%)	25 (14.3%)	0.760
28^{+}–34	22 (15.2%)	27 (15.4%)	0.946
34^{+}–36^{+6}	25 (17.2%)	30 (17.1%)	0.981
⩾ 37	79 (54.4%)	93 (53.2%)	0.811
PPROM	12 (8.3%)	13 (7.4%)	0.799
Preeclampsia	27 (18.6%)	30 (17.1%)	0.731
Placenta previa	10 (6.8%)	11 (6.3%)	0.826
Placental abruption	12 (8.3%)	15 (8.6%)	0.925
Postpartum hemorrhage	14 (9.7%)	16 (9.1%)	0.876

N: number, PPROM: preterm prelabor rupture of membranes, IVF: in vitro fertilization, SC: spontaneous conception, P: probability.

Are all those risks consequence of MAR or multiple pregnancies per se

Table 2 Congenital anomalies in assisted-reproduction twin cohort studies.

Publication and country	Study type and time period	Treatment type and cases	Outcomes
Pinborg et al. (2004) Denmark	Cohort study of IVF singletons and twins; 1995–2000	IVF/ICSI; 3393 twins and 5130 singletons	No differences in any malformation rates
Olson et al. (2005) USA	Cohort study of singletons and multiple gestations; 1989–2002	IVF and IUI; 736 twins versus 909 singletons	No difference in birth defects
Zhu et al. (2006) Denmark	Cohort study of singletons and twins; 1997–2003	Various; 1690 assisted-reproduction twins and 1366 spontaneous twin controls	No difference in malformation rates-reproduction
Ben-Ami et al. (2011) Israel	Cohort study of singletons and twins; 1998–2009	Various; 801 assisted-reproduction twins and 883 twin controls	Increased risk for anencephaly in assisted-reproduction twins due to synergistic effect between twinning and assisted reproduction treatment
Davies et al. (2012) Australia	Cohort study of singletons and multiple gestations; 1986–2002	Various; 1830 assisted-reproduction multiple gestations and 7591 multiple gestation controls	No significant difference in birth defects

ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination.

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MINI-REVIEW

Do assisted-reproduction twin pregnancies require additional antenatal care?

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Eric Jauniaux, MD, PhD, FRCOG is professor of obstetrics and fetal medicine at the Institute for Women Health, UCL UK. His interests are in placental and fetal development and in particular the pathophysiology of miscarriage and the management of assisted-conception pregnancies. He was awarded a personal chair at UCL in 2002. He is one of the founding editors of RBMOnline. He is the editor/co-editor of 10 books, including Cancer and Pregnancy, Embryonic Medicine and Therapy with Bob Edwards and the first textbook on assisted-conception pregnancies in collaboration with Botros Risk. He is the laureate of three international prices for his research work.

Abstract Iatrogenic twinning has become the main side-effect assisted reproduction treatment. We have evaluated the evidence for additional care that assisted-reproduction twins may require compared with spontaneous twins. Miscarriages are increased in women with tubal problems and after specific treatments. Assisted-reproduction twin pregnancies complicated by a vanishing twin after 8 weeks have an increased risk of preterm delivery and of low and very low birthweight compared with singleton assisted-reproduction pregnancies. Monozygotic twin pregnancies occur at a higher rate after assisted reproduction treatment and are associated with a higher risk of perinatal complications. The incidence of placenta praevia and vasa praevia is increased in assisted-reproduction twin pregnancies. Large cohort studies do not indicate a higher rate of fetal congenital malformations in assisted-reproduction twins. Overall, assisted-reproduction twins in healthy women <45 years of age are not associated with a notable increase in antenatal complication rates and thus do not require additional antenatal care compared with spontaneous twins. The risks of maternal and fetal morbidity and mortality associated with assisted-reproduction twins is only increased in women with a pre-existing medical condition such as hypertensive disorders and diabetes and most of these risks can be avoided with single-embryo transfer.

KEYWORDS: antenatal care, antenatal complications, assisted conception, twin pregnancy

Are all those risks consequence of MAR or multiple pregnancies per se

Table 1 Maternal outcomes.

Outcome	IVF (n = 84)	Spontaneous (n = 139)	Adjusted OR (95% CI)
Hypertensive disorders	14 (16.7)	18 (12.9)	0.91 (0.38–2.18)
Gestational diabetes	10 (11.9)	13 (9.4)	1.56 (0.58–4.25)
Intrahepatic cholestasis	9 (10.7)	18 (12.9)	0.64 (0.24–1.70)
Placenta praevia	2 (2.4)	1 (0.7)	1.29 (0.10–16.92)
Hospitalization >10 days	29 (34.5)	45 (32.4)	0.79 (0.40–1.54)
Post-partum bleeding	5 (6.0)	8 (5.8)	1.19 (0.31–4.50
Delivery at 32–36 weeks	55 (65.5)	76 (54.7)	1.91 (0.99–3.62)
Delivery at 30–31 weeks	4 (4.8)	6 (4.3)	0.71 (0.17–2.96)
Delivery before/at 29 weeks	3 (3.6)	12 (8.6)	0.27 (0.07–1.04)
Premature rupture of membranes	20 (23.8)	30 (21.6)	1.04 (0.50–2.16)

Values are number (%) unless otherwise stated.

Table 2 Perinatal outcomes.

Outcome	IVF (n = 168)	Spontaneous (n = 278)	Adjusted OR (95% CI)
Growth discordance	22 (26.2)	28 (20.1)	1.01 (0.48–2.09)
FGR 5th–10th centiles	24 (14.3)	37 (13.3)	1.04 (0.55–1.96)
FGR <5th centile	17 (10.1)	30 (10.8)	0.83 (0.40–1.69)
Perinatal mortality	2 (1.2)	6 (2.2)	0.52 (0.09–2.85)
Neonatal intensive care	51 (30.4)	64 (23.0)	1.13 (0.69–1.86)
Respiratory distress syndrome	17 (10.1)	25 (9.0)	0.86 (0.42–1.75)
Malformations	19 (11.3)	17 (6.1)	1.30 (0.60–2.82)

Values are number (%) unless otherwise stated.
FGR, fetal growth restriction.

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ARTICLE

IVF twins have similar obstetric and neonatal outcome as spontaneously conceived twins: a prospective follow-up study

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Elena Vasario, born in 1980, graduated in Medicine at the University of Turin in 2005 with full marks. Since 2004 she has attended to the Maternal Fetal Medicine Unit of the S. Anna hospital of Turin, where she is currently doing her residency. She is involved in the management of high-risk pregnancies; in particular she cares for multiple pregnancies in an outpatient clinic. She is also involved in research activities about pre-eclampsia, fetal growth restriction and pregnancies in women with kidney diseases.

Abstract Studies comparing the outcome of spontaneous versus IVF twin pregnancies report heterogeneous results. This may depend on differences in the studied populations and/or in the management approach to twin pregnancy. The aim of the present study was to compare both maternal and perinatal outcomes in dichorionic diamniotic twin pregnancies who where spontaneously conceived or originated by successful homologous IVF. In order to get homogeneous observations, monochorionic twin pregnancies and triplet pregnancies were excluded. Moreover, to avoid any possible bias deriving from differences in the obstetric management, all pregnancies were managed by the same team applying fixed obstetric protocols. The study included 223 twin pregnancies, 84 conceived by IVF and 139 spontaneously conceived. Overall, maternal and perinatal outcomes were similar in the two groups: no significant differences were observed as far as gestational age at delivery, birthweight, perinatal morbidity and mortality, and rate of malformations were concerned. The rate of Caesarean section was slightly, but not significantly, higher in IVF pregnancies. In conclusion, the outcome of IVF twin pregnancies is comparable to that of spontaneously conceived twin pregnancies, provided that the same management criteria are applied.

KEYWORDS: in-vitro fertilization, in-vitro fertilization outcome, neonatal outcome, obstetric outcome, pregnancy management, twin pregnancy

Prevention

- Redifining success (BEST concept)
  - Birth emphasizing singleton at term
- eSET implementation
- Good monitoring, legislation end reimbirsment
- National and international strategies for reducing multiple births
- Adequate antenatal care

Single Embryo Transfer – facts

Greatest concern – Does the live birth rate declines

- Recent randomised controlled trials comparing live birth and multiple pregnancy rates following SET versus DET confirm a reduction in live birth rates per embryo replacement procedure but a virtual elimination of twins.
- The reduction in pregnancy rate associated with eSET does not appear to persist following subsequent transfer of a frozen embryo, so that cumulative pregnancy rates are not significantly less than those of DET.
- If carefully chosen, couples at high risk of multiple pregnancy may therefore benefit from eSET.

Table III. Elective single embryo transfer (eSET) versus double embryo transfer (DET): results from observational studies of fresh cycles

Study	*n*	eSET			DET		
		Pregnancy rate[a]	Delivery rate	Twin rate[b]	Pregnancy rate[a]	Delivery rate	Twin rate[b]
Vilska *et al.*, 1999	816	22/74 (29.7)	18/74 (24.3)	0	218/742 (29.4)	NA	52/218 (23.9)
Tiitinen *et al.*, 2003	1494	162/470 (34.4)	128/470 (27.2)	2/128 (1.6)	376/1024 (36.7)	275/1024 (26.9)	76/275 (27.6)
Gerris *et al.*, 2002	1152	105/299 (35.1)	NA	1/105 (0.9)	309/853 (36.2)	NA	109/309 (35.3)
De Sutter *et al.*, 2003	2898	163/579 (28.2)		1/163 (0.6)	734/2319 (31.7)		223/734 (30.4)
Catt *et al.*, 2003	385	49/111 (44.1)		1/49 (2.0)	161/274 (58.8)		71/161 (44.1)
Gerris *et al.*, 2004	367	83/206 (40.3)	77/206 (37.4)	0	65/161 (40.4)	59/161 (36.6)	20/59 (30.8)
Martikainen *et al.*, 2004	1111	107/308 (34.7)	86/308 (27.9)	1/86	255/803 (31.8)	NA	NA
Total	8263	691/2047 (33.8)	309/1058 (29.2)	6/626 (1.0)	2118/6176 (34.3)	334/1185 (28.2)	551/1756 (31.4)

Bergh et al.

Pandian Z, Marjoribanks J, Ozturk O, Serour G, Bhattacharya S. Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection.

Cochrane Database Syst Rev. 2013 Jul 29;

- Fourteen RCTs were included in the review (2165 women).
- The cumulative live birth rate after one cycle of DET was not significantly different from the rate after repeated SET (OR 1.22, 95% CI 0.92 to 1.62)
- single cycle of DET was compared with a single cycle of SET and live birth rate was significantly higher in the DET group (OR 2.07, 95% CI 1.68 to 2.57)
- The multiple pregnancy rate was significantly higher in the DET group (OR 30.54, 95% CI 7.46 to 124.95)
- compared DET versus transfer of three or four embryos. Live birth rates did not differ significantly between the groups for any comparison, but there was a significantly lower multiple pregnancy rate in the DET group than in the three embryo transfer (TET) group (OR 0.36, 95% CI 0.13 to 0.99)
- **AUTHORS' CONCLUSIONS:**

  In a single fresh IVF cycle, single embryo transfer is associated with a lower live birth rate than double embryo transfer. However, there is no evidence of a significant difference in the cumulative live birth rate when a single cycle of double embryo transfer is compared with repeated SET (either two cycles of fresh SET or one cycle of fresh SET followed by one frozen SET in a natural or hormone-stimulated cycle)

SET – prerequisites for implementation

SET

Cryopreservation of spare embryos

High-quality instruments,
models and methods of embryo selection

Good public policy
funding
(reimbursement policy)

Can it be done – YES

Perinatal outcome is better with SET

Reproductive BioMedicine Online (2010) 20, 836–842

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ARTICLE

Cumulative live-birth delivery after IVF/ICSI since the progressive introduction of single-embryo transfer

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Diane De Neubourg graduated from Medical School at the University of Antwerp in 1990. She became a specialist in Obstetrics and Gynecology in 1995 at the University of Antwerp. She obtained a Master in Medical Sciences degree in Assisted Reproduction Technologies in 1996 at the University of Nottingham and obtained her PhD thesis at the University of Ghent on Single embryo transfer in 2005. Presently, she is the medical director of the Centre for Reproductive Medicine of the ZNA Middelheim Hospital Antwerp. Her fields of interest are reproductive endocrinology and assisted reproduction technology.

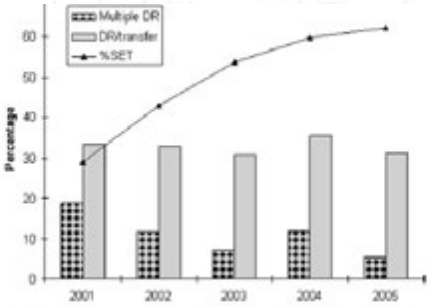

Figure 1 Evolution of delivery rate (DR), multiple delivery rate and percentage of single-embryo transfer (SET) from 2001 to 2005.

Human Reproduction, Vol.27, No.12 pp. 3609–3615, 2012
Advanced Access publication on September 17, 2012 doi:10.1093/humrep/des315

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Single embryo transfer reduces the risk of perinatal mortality, a population study

Elizabeth A. Sullivan[1,*], Yueping A. Wang[1], Irene Hayward[1], Georgina M. Chambers[1], Peter Illingworth[2], John McBain[3], and Robert J. Norman[4]

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Submitted on March 19, 2012; resubmitted on June 21, 2012; accepted on July 12, 2012

STUDY QUESTION: Do births following single embryo transfers (SET) have a reduced risk of perinatal mortality compared with those following double embryo transfers (DET)?

SUMMARY ANSWER: SET is associated with reduced risk of perinatal mortality compared with DET.

WHAT IS KNOWN ALREADY: Fetal, neonatal and perinatal mortality are important indicators for monitoring pregnancy and childbirth, particularly for births following assisted reproductive technology (ART) treatments. Following the introduction of SET, there has been a decline in the perinatal mortality rate (PMR) among babies born after ART in Australia and New Zealand.

STUDY DESIGN, SIZE, DURATION: This population study (census) included 50 258 births of ≥20 weeks gestation and/or ≥400 g of birthweight following embryos transfer cycles in Australia and New Zealand during the period 2004–2008.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The PMR was calculated according to the number of embryos transferred and other demographic and treatment-related factors. Perinatal deaths were defined as the number of fetal deaths (stillbirths) plus the number of neonatal deaths (deaths that occur before 28 days after birth).

MAIN RESULTS AND THE ROLE OF CHANCE: The PMR was 16.2 per 1000 births (n= 813). Of the 813 perinatal deaths, 630 were fetal deaths and 183 neonatal deaths. Twins had a significantly higher PMR (27.8 per 1000 births) than singletons (12.4 per 1000 births). The risk of perinatal mortality for all births following DET was 53% higher than for all births following SET (adjusted risk ratio 1.53, 95% confidence interval (95% CI): 1.29–1.80). Births following fresh DET had a 58% increased risk of perinatal mortality compared with births following fresh SET (risk ratio 1.58, 95% CI: 1.32–1.90).

LIMITATIONS, REASONS FOR CAUTION: Information on outcomes was missing from <1% of clinical pregnancies recorded in Australian and New Zealand Assisted Reproduction Database for the study period. There are no data on the timing of fetal death, the cause of perinatal death or on late termination of pregnancy at ≥20 weeks' gestation.

WIDER IMPLICATIONS OF THE FINDINGS: Double and higher order embryo transfer is associated with a higher risk of perinatal mortality when compared with SET. The number of embryos transferred is determined by the clinician with consent of the patient and is a modifiable treatment factor. SET should be advocated as the first-line management in ART as it is the single most effective public health intervention for preventing excess perinatal mortality among ART pregnancies.

Single embryo transfer reduces the risk of perinatal mortality in IVF

- The study she described included 50,258 births which were of more than 20 weeks gestation and/or 400 grams birthweight following IVF and ICSI pregnancies.
- Births following the transfer of two embryos had a significantly higher perinatal mortality rate than births following SET (19.1 per 1000 births and 13.2 per 1000 births).
- The risk of perinatal mortality for all births following two embryo transfer was 53% higher than those following SET.
- 74% higher risk of perinatal mortality than births following fresh SET.

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SCIENCE MOVING PEOPLE MOVING SCIENCE

Press information

from the 28th Annual Meeting of the
European Society of Human Reproduction and Embryology

Embargo: 09.30 hrs EEST (07.30 London), Wednesday 4 July 2012

This press release is in support of a news briefing by Professor Elizabeth Sullivan at 9.30 am (EEST) on Wednesday 4 July 2011 [Hamidiye, ICC building, Floor B2]

Single embryo transfer reduces the risk of perinatal mortality in IVF

Prevention of multiple pregnancies; the Belgian project, Willem Ombelet et al. 2004

Women ≤ 35 years old		
1st attempt	⇨	single embryo transfer (SET)
2nd attempt	⇨	single embryo transfer (SET) if one or more top-embryos are available
	⇨	transfer of two embryos if no top-embryo is available
3rd – 6th attempt	⇨	maximum two embryos transferred
Women > 35 and ≤ 39 years old		
1st and 2nd attempt	⇨	maximum two embryos transferred
3rd – 6th attempt	⇨	maximum three embryos transferred
Women > 39 and ≤ 42 years old		
1st – 6th attempt	⇨	no limit for number of embryos transferred
Women > 42 years old		
No reimbursement		

- Then we found out that the money (just from neo natal costs) we could save with the reduction of multiple pregnancies, reduction of twin pregnancies by 50% and triplet pregnancies to almost zero, would be enough to reimburse the laboratory cost of all patients for at least six cycles.

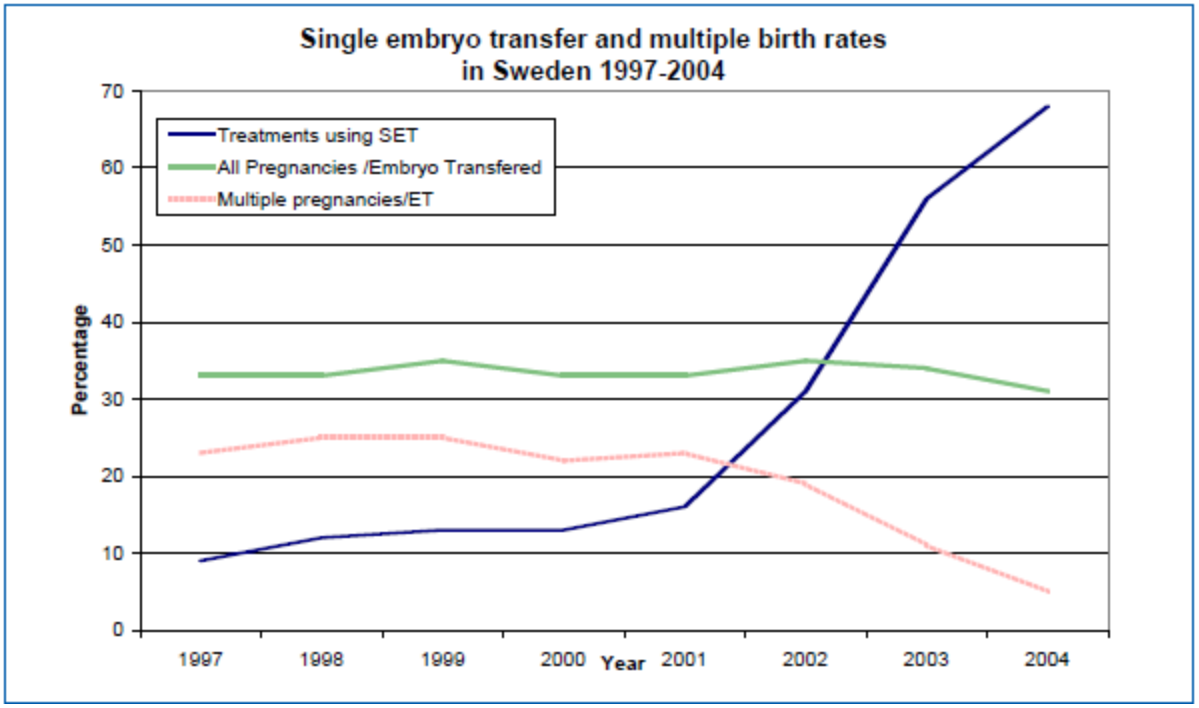
Slovenian model

- 6 full cycles (fresh and FER) REIMBURSED + 4 Cycles after delivery
- SET is obligatory in first 2 cycles if good quality embryos are available
- Age limit is 43 years

"You can have as many embryos back as you like, only one at a time."

Dr Karl Nygren, Sweden, advice to IVF patients

Correlation between eSET rates and multiple rates



- Doing 30% eSET cycles leads to a twin birth rate of around 20%;
- Doing 50% eSET cycles leads to a twin birth rate of around 10%;
- Doing 70% eSET cycles leads to a twin birth rate of around 5%.

Human Reproduction Update, Vol.17, No.1 pp. 107–120, 2011
Advanced Access publication on July 15, 2010 doi:10.1093/humupd/dmq028

human reproduction update

Global variations in the uptake of single embryo transfer

Abha Maheshwari, Siriol Griffiths, and Siladitya Bhattacharya*

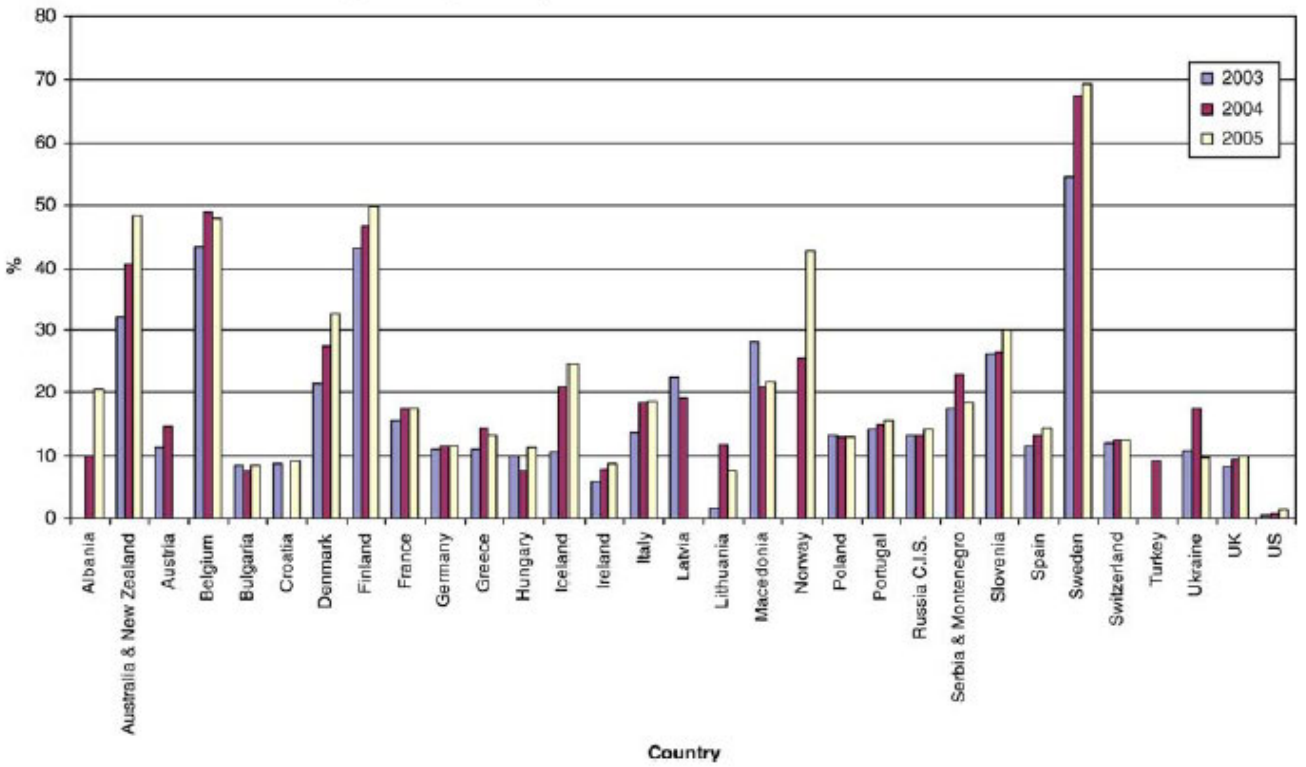
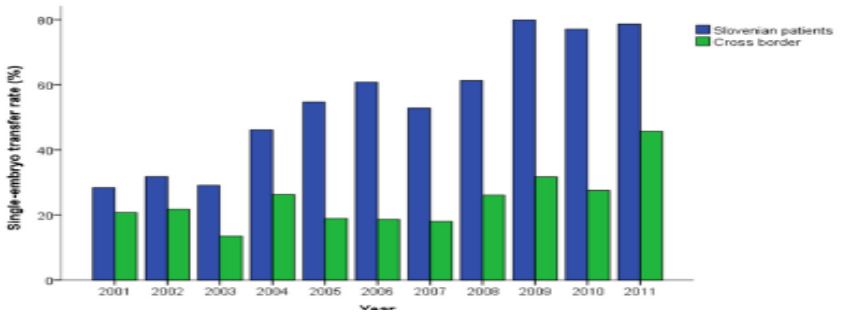
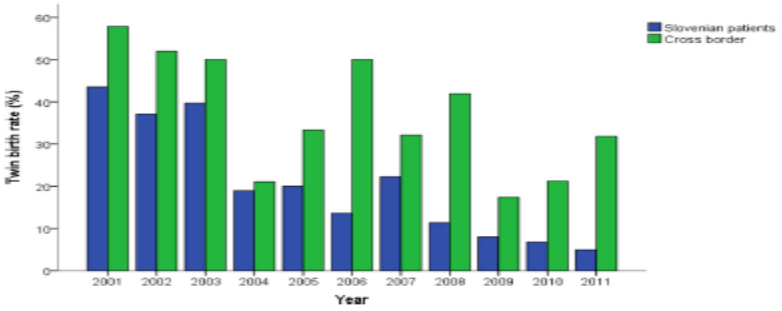


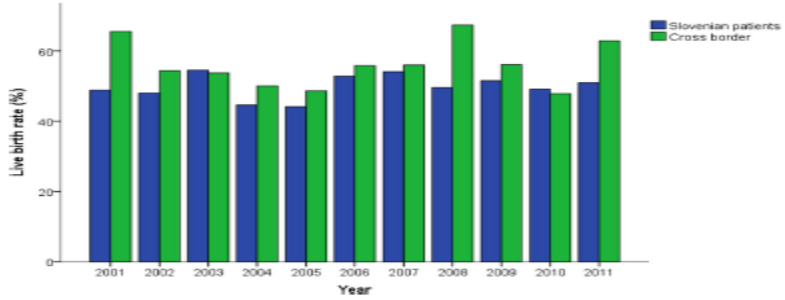
Figure 1 SETs as a proportion of all embryo transfers in 2003–2005.

Slovenian model: Multiple pregnancy rate before and after new reimbursement model dropped from 24,4 % to 6,7%.

At the same time cross border patients (no reimbursement applied) remained high multiple pregnancy rate 23,1% vs. 6,7%







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ARTICLE

Comparison of embryo transfer strategies and assisted reproduction outcome in Slovenian and cross-border patients

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Jure Knez obtained his MD degree from the University of Ljubljana Medical Faculty in 2008. He commenced his residency in obstetrics and gynaecology at University Medical Centre in Maribor in 2009, where he continues his research work in the field of infertility and andrology as a PhD student. Under the mentorship of Professor Dr Veljko Vlaisavljević, he has been involved in several research projects on assisted reproduction, male infertility, embryo transfer and cross-border reproductive care.

Abstract A reduction in the number of embryos transferred is the most important step in decreasing multiple gestation rates after medically assisted reproduction. Slovenia has implemented insurance company regulations that regulate single-embryo transfer in selected good-prognosis couples. The aim of the present study was to evaluate its effects on the Slovenian population compared with cross-border patients, who are not affected by the insurance company policy. Ultimately, 2403 couples undergoing IVF or intracytoplasmic sperm injection were included in the retrospective analysis. Patients were classified according to their origin. The decision about the number of embryos transferred and the treatment success were evaluated. The implementation of the policy favouring single-embryo transfer resulted in a significant decrease in the twin birth rate in Slovenian patients (24.4% before policy versus 6.7% after policy implementation, $P < 0.001$). Although in cross-border patients twin birth rates have declined through the study period, they remained significantly higher compared with Slovenian patients (23.1% versus 6.7%, $P < 0.001$). The data demonstrate that insurance company policies favouring single-embryo transfer are an effective tool in decreasing multiple gestation rates. Similar mechanisms should be implemented in the cross-border patient population.

KEYWORDS: cross-border reproductive care, single-embryo transfer, twin birth rate

Our results

Devastating facts

- Average number of embryos transferred around 2.8
- eSET practicaly incidental, conpulsatory SET less than 5%
- **TET around 80%**
- Poor reimbursement (2 Cycles, no Cryo covered, and no SET obligation)
- Broad Cryo program just started
- Legislation allows TET
- Poor patient education

Consequence

Sample size	1325 cycles
Clinical pregnancy rate pre ET	33.01%
Deliveries per ET	25.89%
Singleton deliveries	55.37%
Twin deliveries	39.93%
Triplet deliveries	4.70%
Mulitple deliveries	**44.63%**

Our results on perinatal outcome in IVF/ICSI vs. spontaneously concieved multiple pregnancies (Deliveries 2008-10)

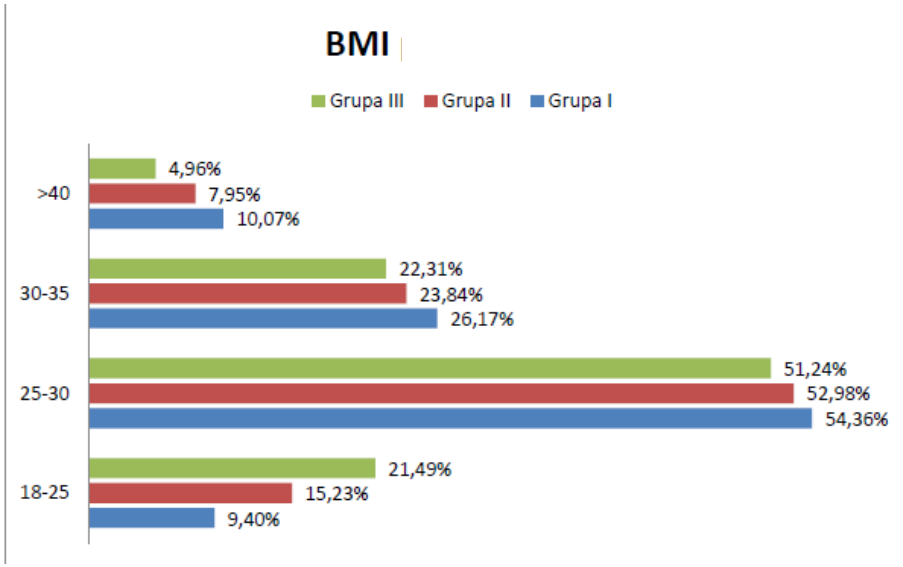
- Group I - multiple ART – 163
- Grupa II - multiple non ART – 174
- Grupa III - singleton ART – 155

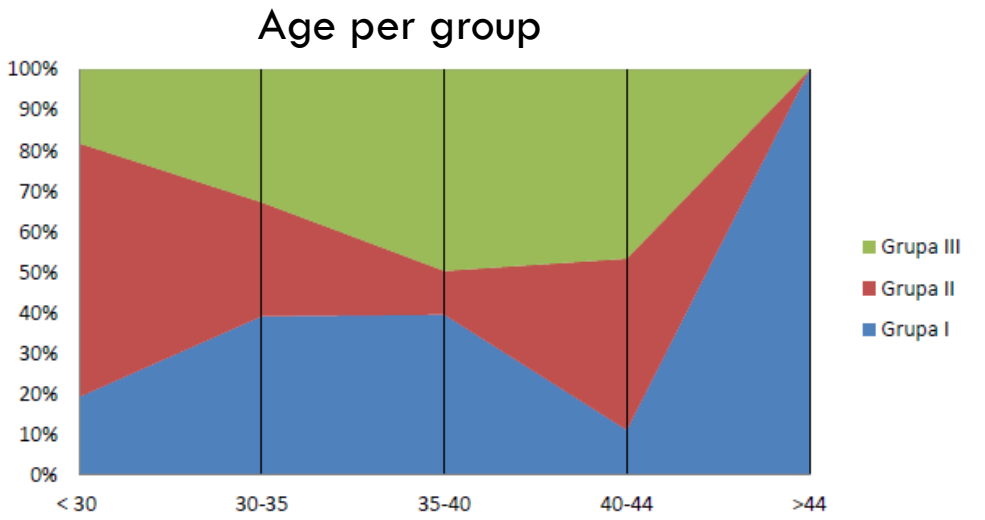
$\sum = 492$

		Spontaneous conception	%	IVF	%	Total
Multiple pregnancies	Twins	171 (IIA)	55,16%	139 (IA)	44,84%	310 (91,99%)
	Triplets	3 (IIB)	11,11%	24 (IB)	88,89%	27 (8,01%)
	Total	174 (II)	51,63%	163 (I)	48,37%	337
Singleton pregnancies		0	0%	155 (III)	100%	155

Results - demographic and anthropometric characteristics

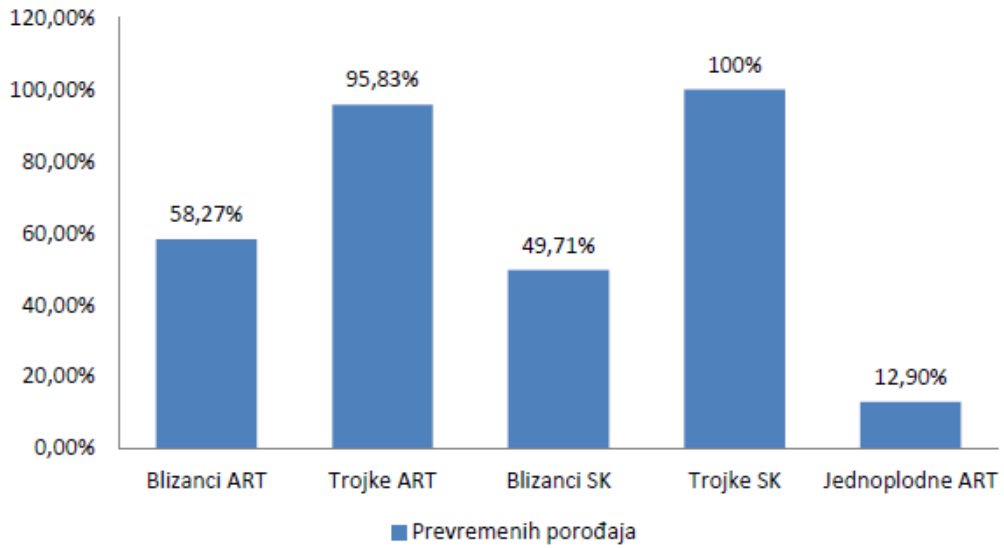
	Age of woman	BMI
Group I	33,02±3,98	29,20±3,81
Group II	28,85±5,04	28,44±5,36
Group III	33,55±3,81	27,69±4,49
P	<0,0001	0.028





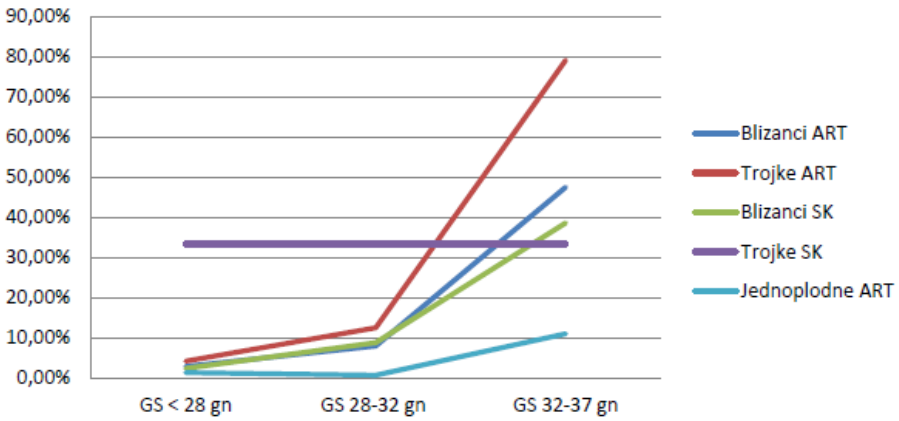
Results - gestational age

	Pregnancy gw	GS < 28 gw	GA 28-32gw	GA 32-37gn	Preterm delivery
Multiple ART	35.29±3.13	3.07%	8.59%	52.15%	63.80%
Multiple SC	35.99±3.21	2.87%	9.20%	38.51%	50.57%
Singleton ART	38.26±2.21	1.29%	0.65%	10.97%	12.90%
P	<0.0001	<0,0001	<0.0001	<0.0001	<0.0001

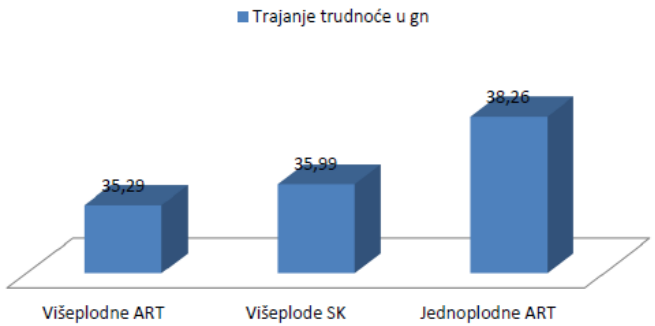


Results - gestational age

Categories of premature births by group



Duration of pregnancy in gestation weeks

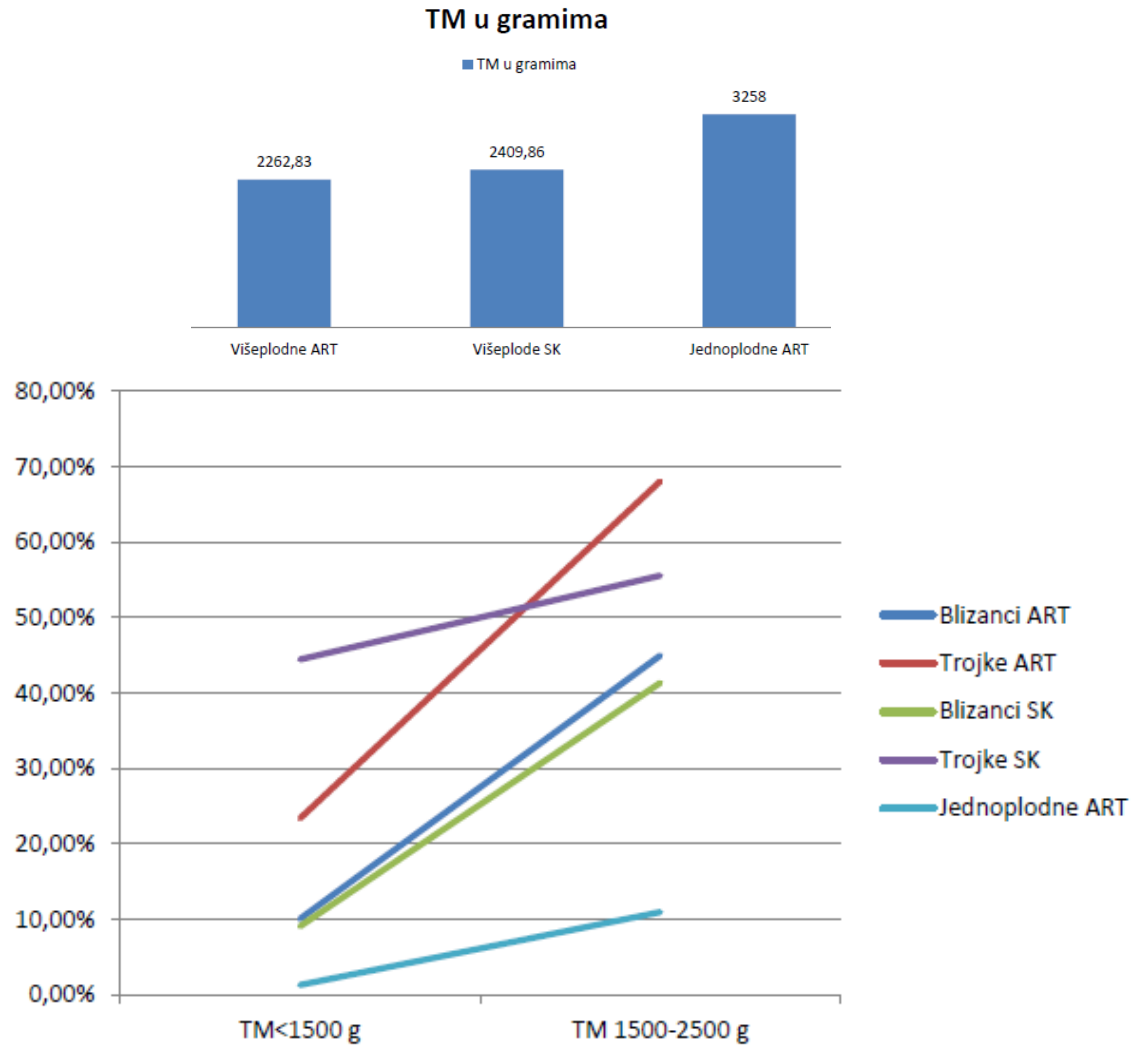


Results – Infants body weight

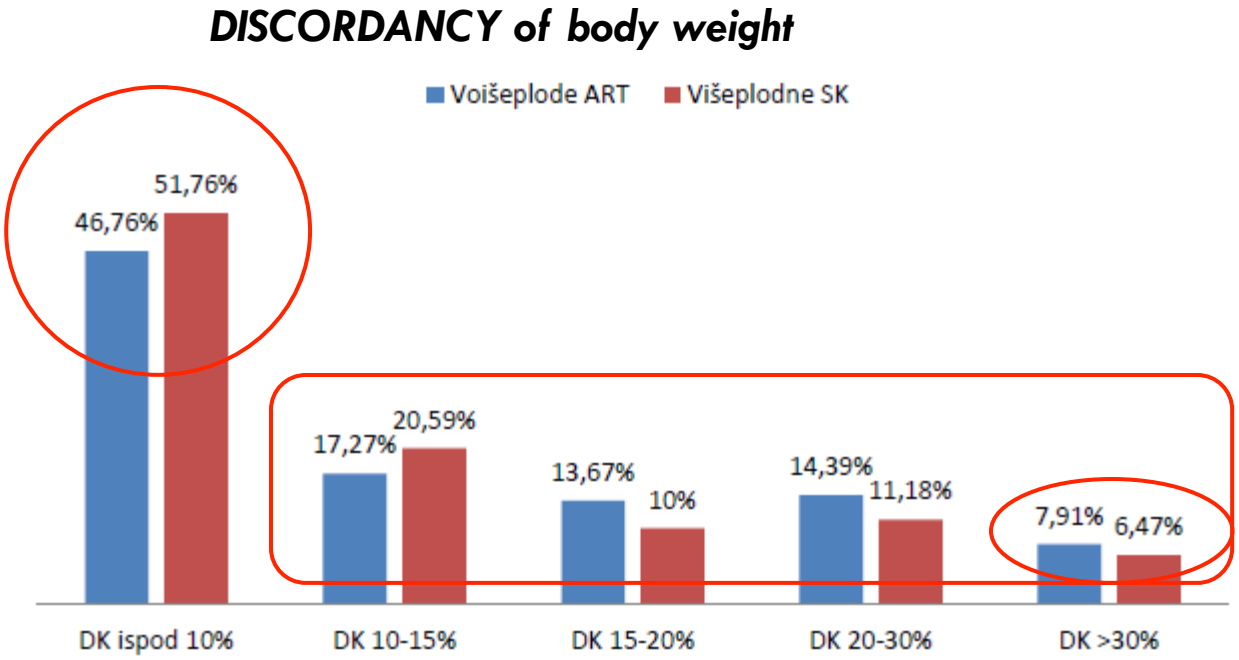
	BM in grams	BM<1500 g	BM 1500-2500 g
Multiple ART	2262.83±661.74	13.43%	49.71%
Multiple SC	2409.86±651.89	10.00%	41.71%
Singleton ART	3258±666.50	1.29%	10.97%
p	<0.0001	<0.0001	

	BM in grams	BM<1500 g	BM 1500-2500 g
Twins ART	2374.28±653.4	10.07%	44.96%
Triplets ART	1832.50±500.35	23.39%	68.06%
Twins SK	2433.20±636.85	9.09%	41.35%
Triplets SK	1525±631.56	44.44%	55.56%
Singleton ART	3258.00±666.5	1.29%	10.97%
p	<0.0001	<0.0001	<0.0001

Results – Infants body weight



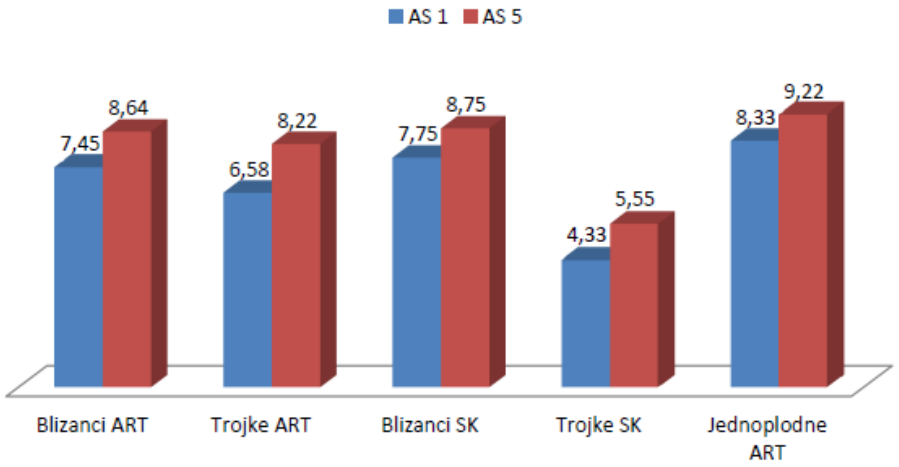
No statistically significant differences, p=0,634



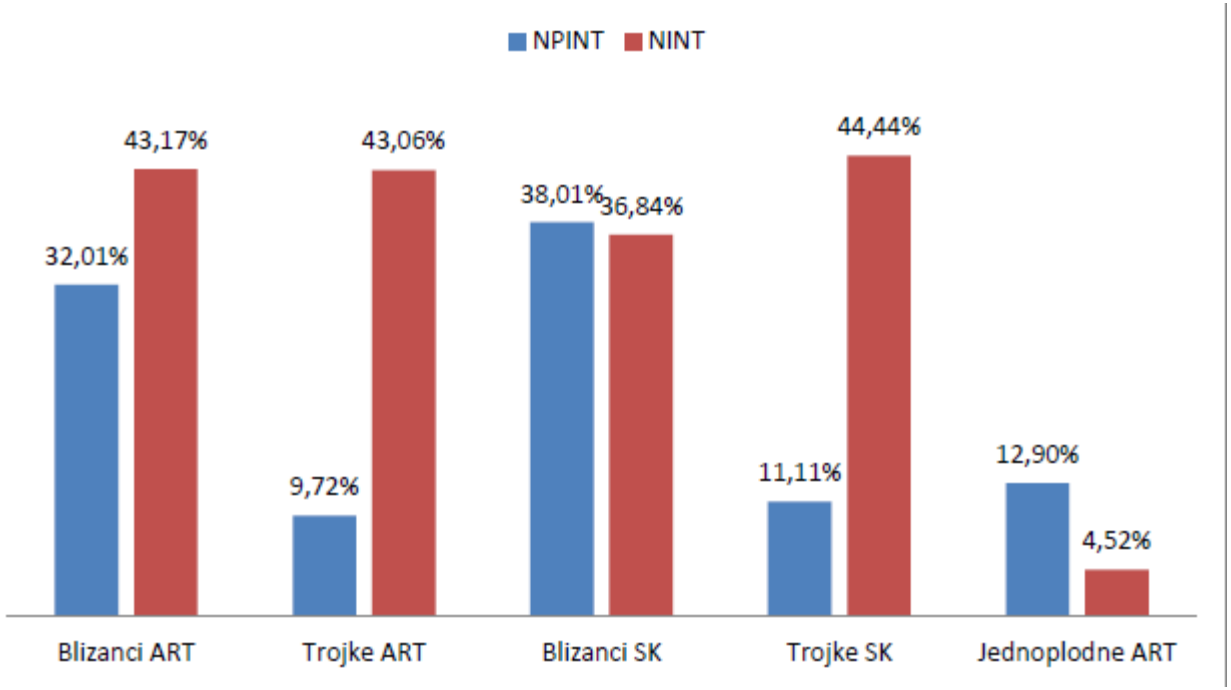
Rezultati – Apgar score p<0,0001

	AS1 0-3	AS1 4-6	AS1 7-10	AS5 0-3	AS5 4-6	AS5 7-10
Blizanci ART	7.97%	13.77%	78.26%	2.92%	6.57%	90.51%
Trojke ART	12.50%	26.39%	61.11%	0%	11.27%	88.73%
Blizanci SK	4.42%	16.81%	78.76%	1.76%	4.71%	93.53%
Trojke SK	33.33%	44.44%	22.22%	22.22%	11.11%	66.67%
JednoplodneART	1.94%	3.23%	94.84%	1.94%	0%	98.06%
p vrednost	<0.0001			<0.0001		

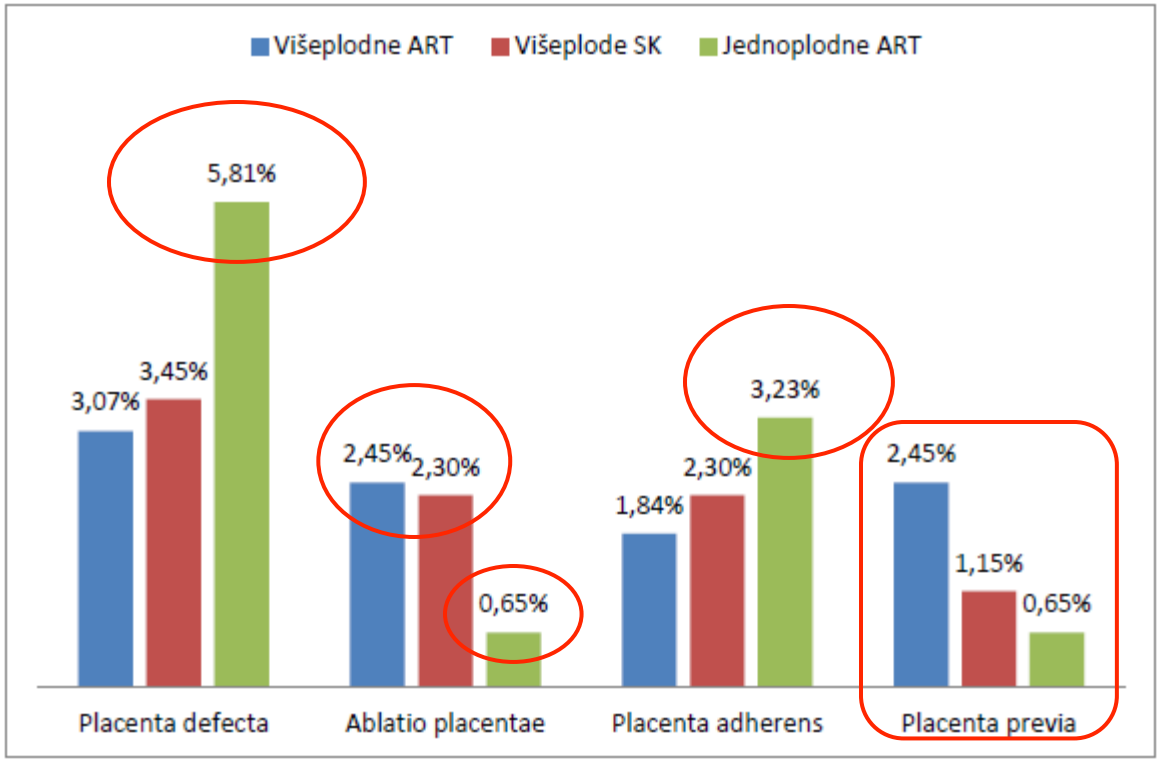
Apgar score



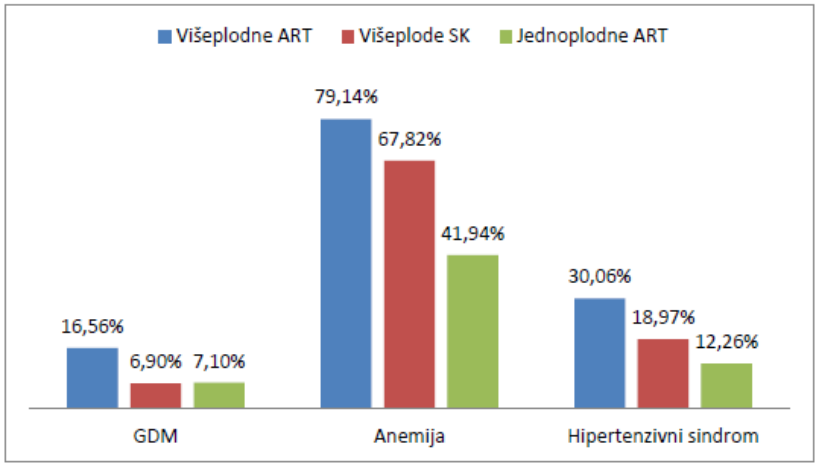
Neonatal intensive care (NICU)
Neonatal semi intensive care (NSICU)



Complications from the placenta



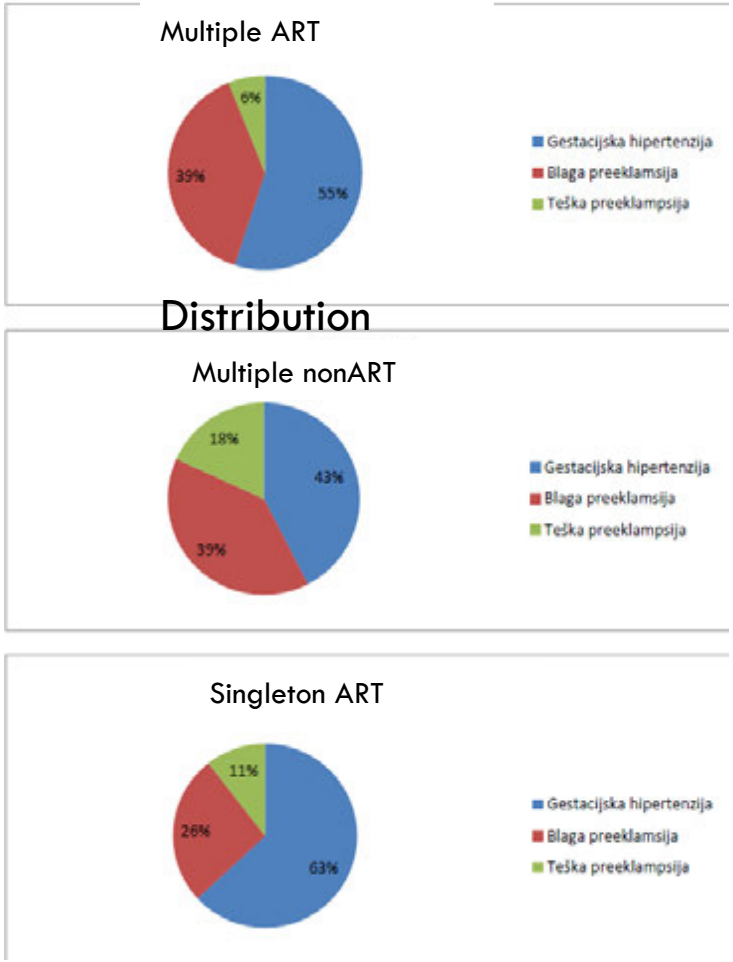
Complications in pregnancy



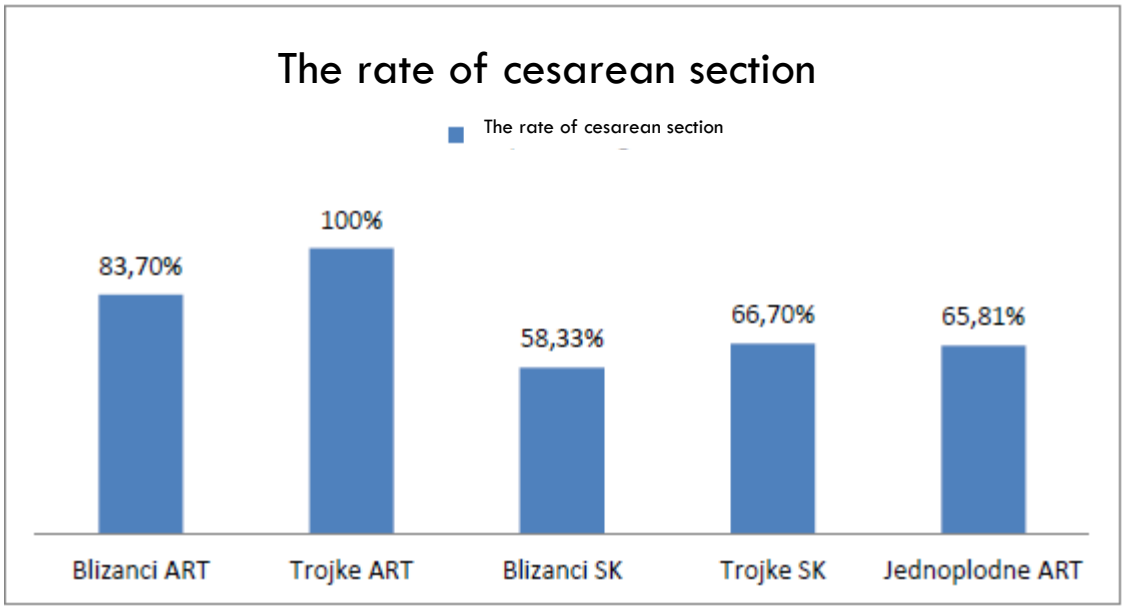
	GDM	Anemia	Hypertensive syndrom
Twins ART	15.11%	78.42%	25.90%
Triplets ART	25.00%	83.33%	54.17%
Twins SK	7.02%	67.84%	19.30%
Triplets SK	0%	66.67%	0%
Singleton ART	10.16%	41.94%	12.26%
p	0.0099	<0.0001	0,0014

Complications in pregnancy

Frequency	Gestation hypertension	Mild preeclampsia	Severe preeclampsia
Twins ART	13.67%	10.79%	1.44%
Triplets ART	33.33%	16.67%	4.17%
Twins SK	8.19%	7.60%	3.51%
Triplets SK	0%	0%	0%
Singleton ART	7.74%	3.23%	1.29%
p	0.0014		



Method of delivery



Take home massages

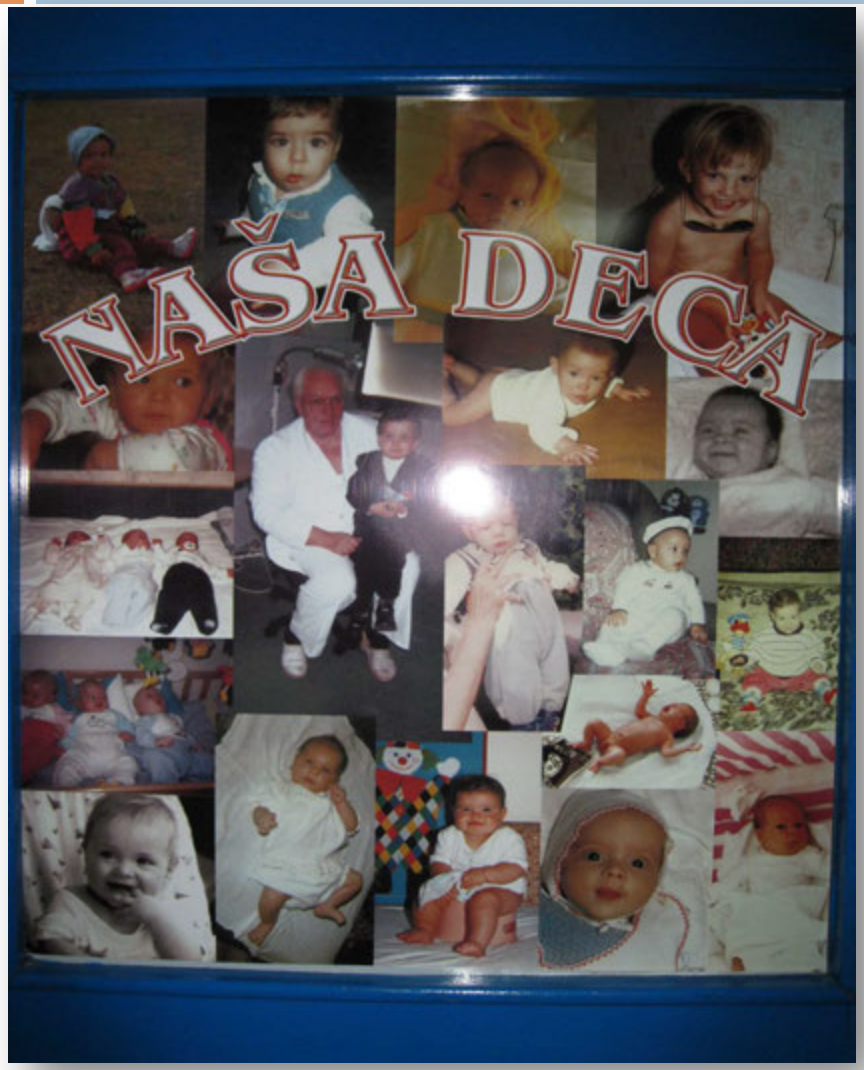
- Multiple births after IVF/ICSI procedures are the main problem of medically assisted reproduction, with numerous health risks for mother, child, healthcare system and society.
- Their reduction should be the main goal of every participant in our practice.
- Best way to achieve this is by implementing SET, as done successfully in numerous countries, without reduction in live birth rate, but with significant reduction in multiple birth rate.
- This implementation requires not just involvement of health care system but whole society with all its potentials must be included in dealing with this problem.
- Good reimbursement politics, monitoring, and legislation of MAR procedures as well as functional vitrification program, patient and health care professionals education are prerequisite for this.

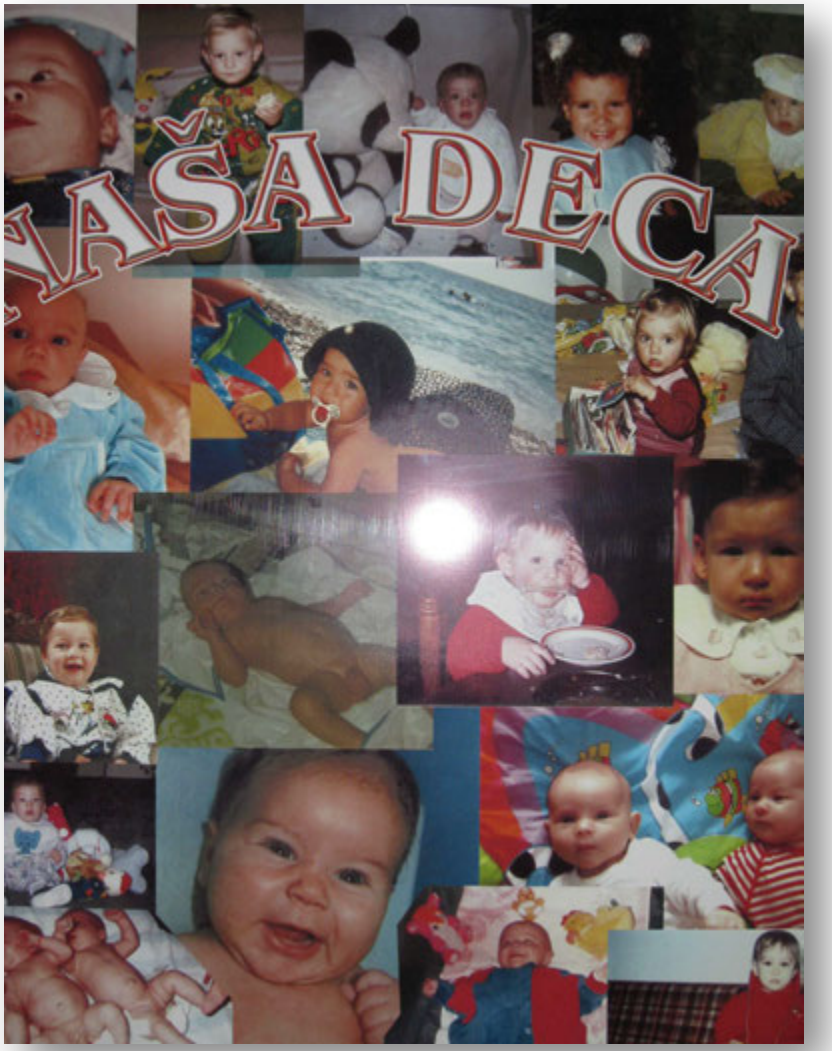
Jan Gerris - quotes

- *'A positive pregnancy test is not a success; a healthy baby is. Two healthy babies at the same time are a success as well, but obstetricians know that it is difficult to predict which multiple will end well and which not. … The problem is not any one particular twin [pregnancy] ending in the birth of two perfect children, but the epidemic size of the complications.'*

- *There is overwhelming evidence that multiple pregnancies lead to much increased morbidity and mortality for mothers and children and can have negative consequences for parents and families.*

Clinical centre of Vojvodina





Department of Human reproduction, Novi Sad

Thank You