Prevention of multiple pregnancies in ART and its influence on live birth rates

Prof. Dr. Diane De Neubourg
Center for Reproductive Medicine, Antwerp University Hospital
Faculty of Medicine, University of Antwerp
Belgium

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Why do we have to prevent multiple pregnancies?

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Why do we have to prevent multiple pregnancies?

- **= The most important complication of assisted reproduction technology (ART) with big differences between countries**.

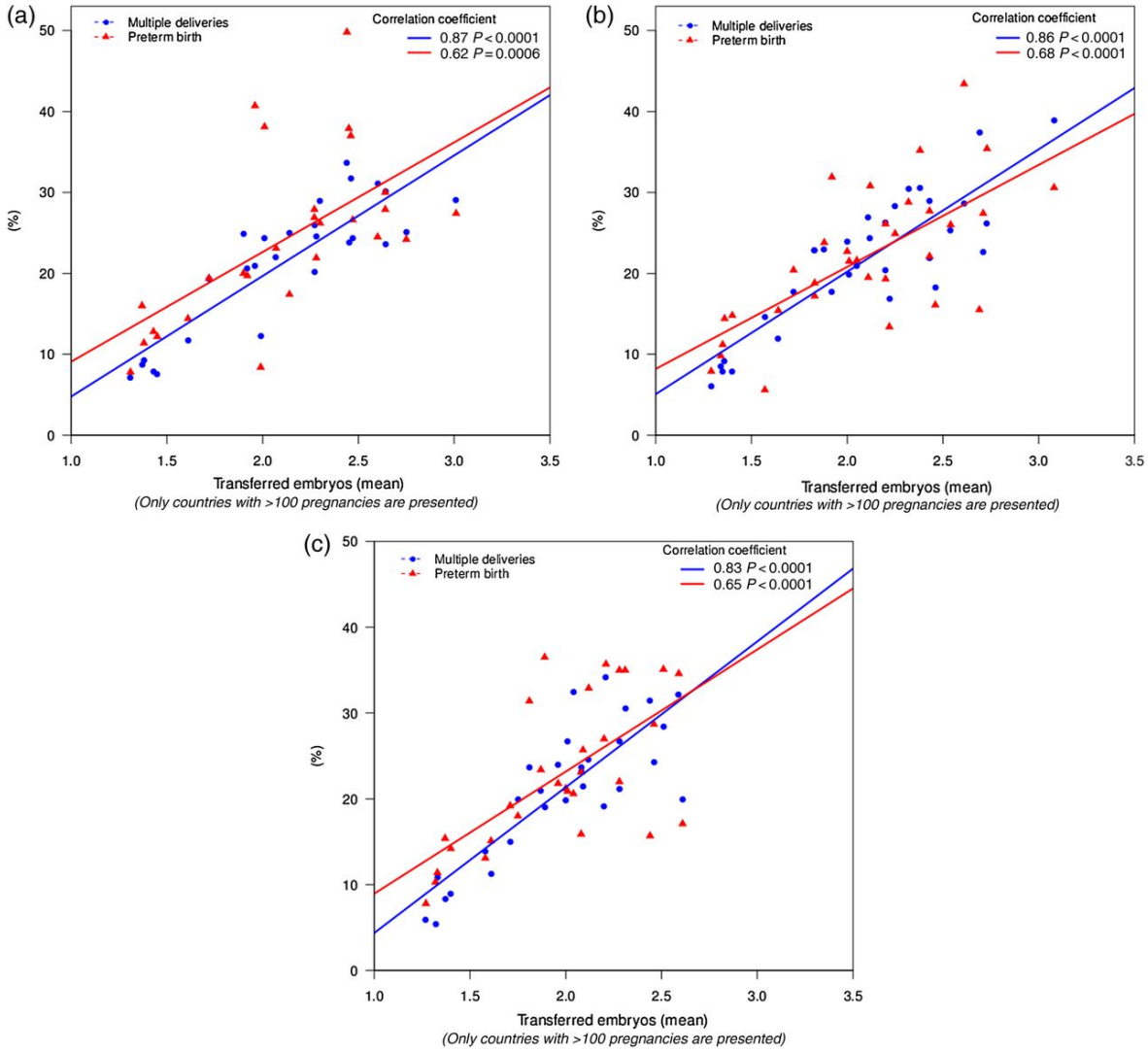
- **Obstetric**: Preterm delivery, hypertension, preecclampsia and higher risk for caesarean section
- **Neonatal and perinatal**: Neonatal mortality, low birth weight, respiratory distress syndrome, cerebral haemorrhage, necrotizing enterocolitis, visual complications,…
- **Economical**: parents, society, insurance
- **Psychosocial**: parents, children
- **Financial:** parents, society

Why do we have to prevent twin pregnancies?

- Even twin pregnancies show adverse obstetric outcome:
  - ✓ Twins after ART are born 3 weeks earlier and have a birth weight of 1000 g less than dan ART singletons ➔ **perinatal morbidity and mortality.**

• Stillbirth	x4.0
• Neonatal death	x5.9
• Perinatal death	x4.9
• Cerebral haemorrhage	x5.2
• Respiratory distress syndrome	x6.4
• Necrotizing enterocolitis	x4.5

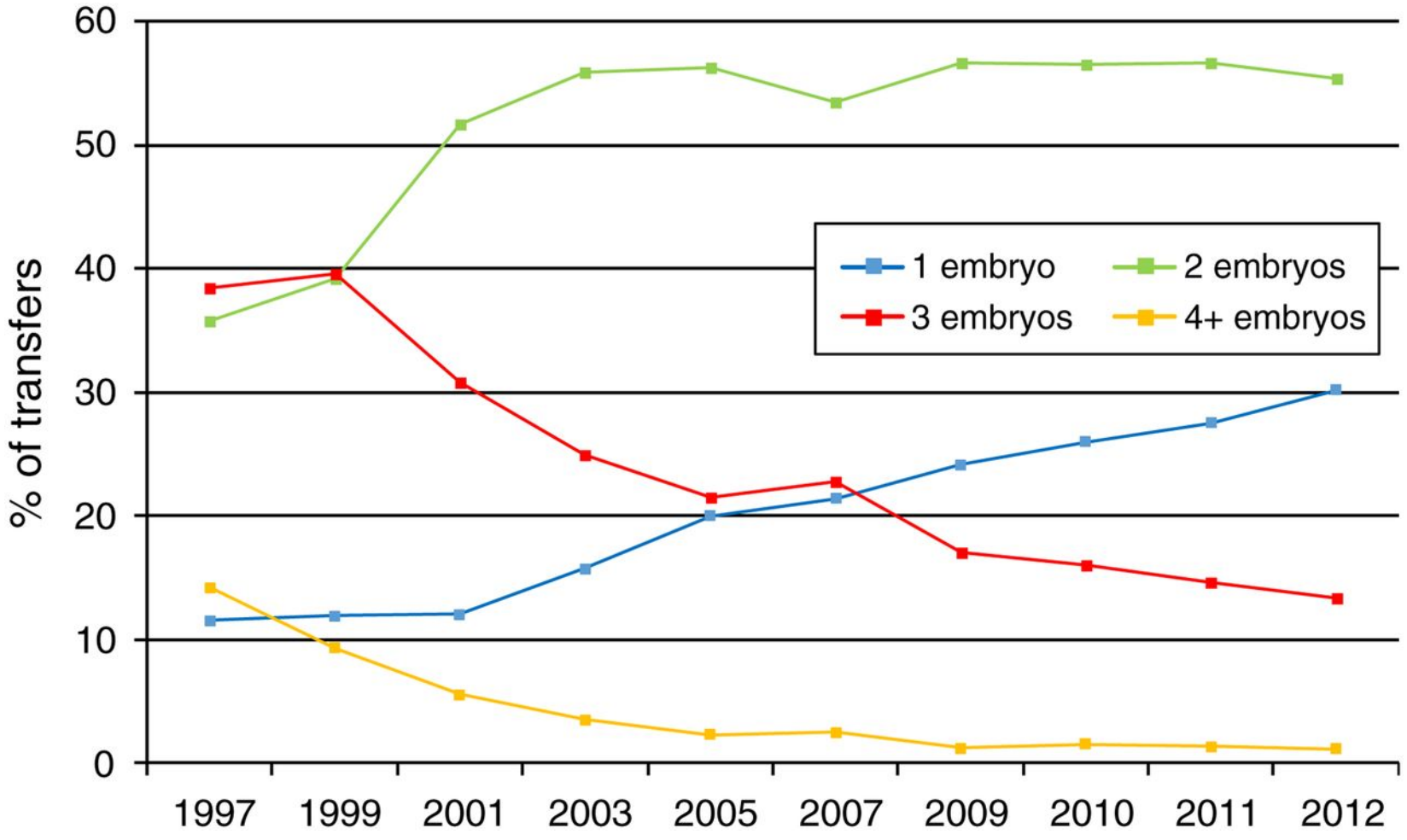
The correlation between rate of multiple deliveries/preterm births and mean number of embryos transferred for year 2008 - 2009 - 2010.



S. Dyer et al. Hum. Reprod. 2016;31:1588-1609

ICMART

Number of embryos transferred in IVF/ICSI fresh cycles in Europe 1997–2012.



The European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) et al. Hum. Reprod. 2016;31:1638-1652

N embryos transferred (fresh cycles) 2012	1	2	3	4+
All	30.2%	55.4%	13.3%	1.1%
Range	9.1- 76.3 %	22.9 - 76.6 %	0 - 56.5 %	0 – 18.6 %

The European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) et al. Hum. Reprod. 2016;31:1638-1652

Deliveries (fresh cycles) 2012	Singleton	Twin	Triplet
All	82.1%	17.3%	0.6%
Range	65.9 - 94.8 %	5.2 - 34.1 %	0 - 4.7 %

The European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) et al. Hum. Reprod. 2016;31:1638-1652

A case study of reducing the incidence of multiple pregnancy in Belgium

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Human Reproduction, Vol.28, No.10 pp. 2709–2719, 2013
Advanced Access publication on July 2, 2013 doi:10.1093/humrep/det269

human reproduction ORIGINAL ARTICLE *Infertility*

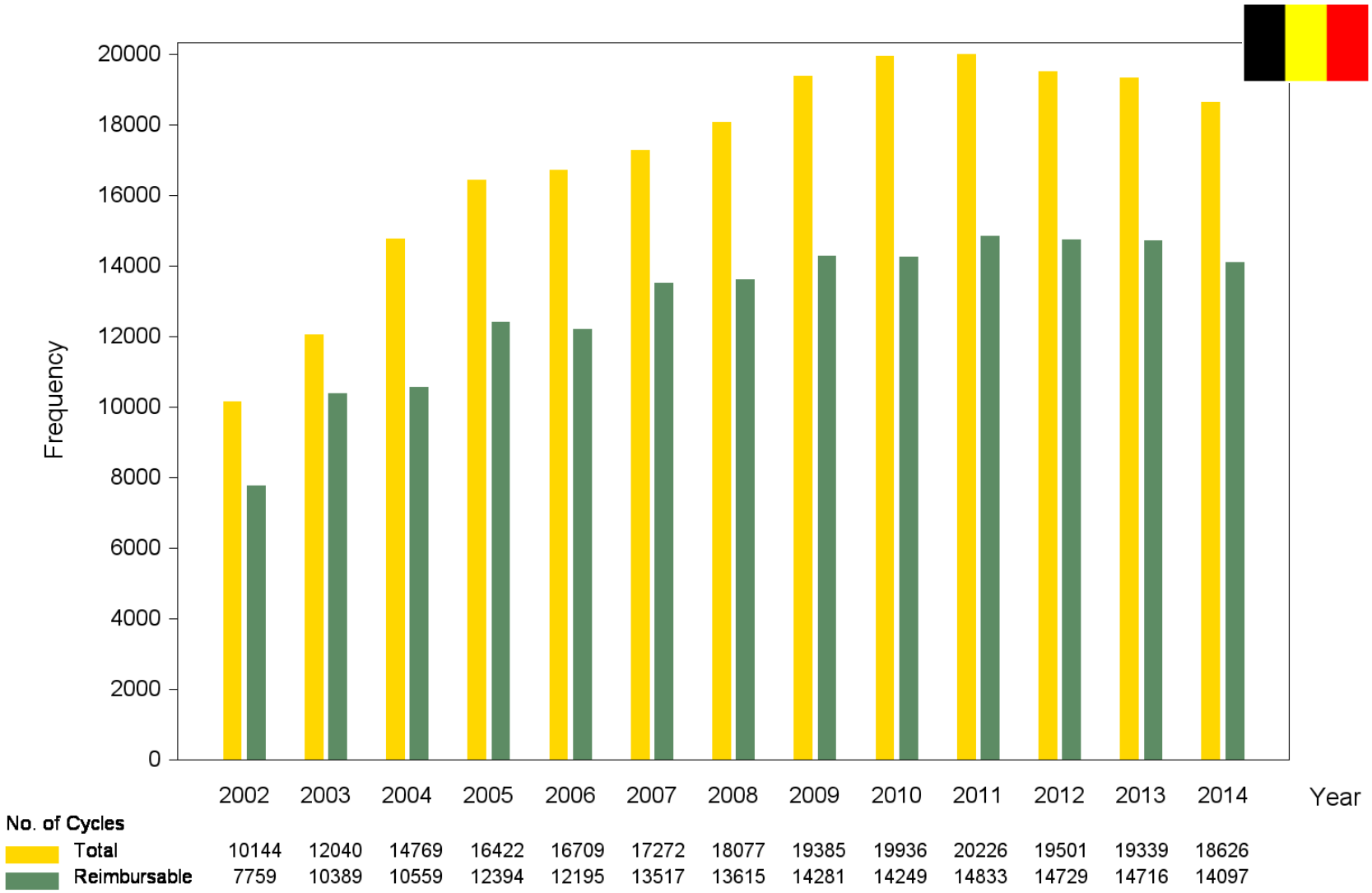
The history of Belgian assisted reproduction technology cycle registration and control: a case study in reducing the incidence of multiple pregnancy

D. De Neubourg[1,2,*], K. Bogaerts[3], C. Wyns[4], A. Albert[5], M. Camus[6], M. Candeur[7], M. Degueldre[8], A. Delbaere[9], A. Delvigne[10], P. De Sutter[11], M. Dhont[11], M. Dubois[12], Y. Englert[9], N. Gillain[5], S. Gordts[13], W. Hautecoeur[14], E. Lesaffre[15], B. Lejeune[16], F. Leroy[17], W. Ombelet[18], S. Perrier D'Hauterive[12], F. Vandekerckhove[11], J. Van der Elst[19], and T. D'Hooghe[1,2]

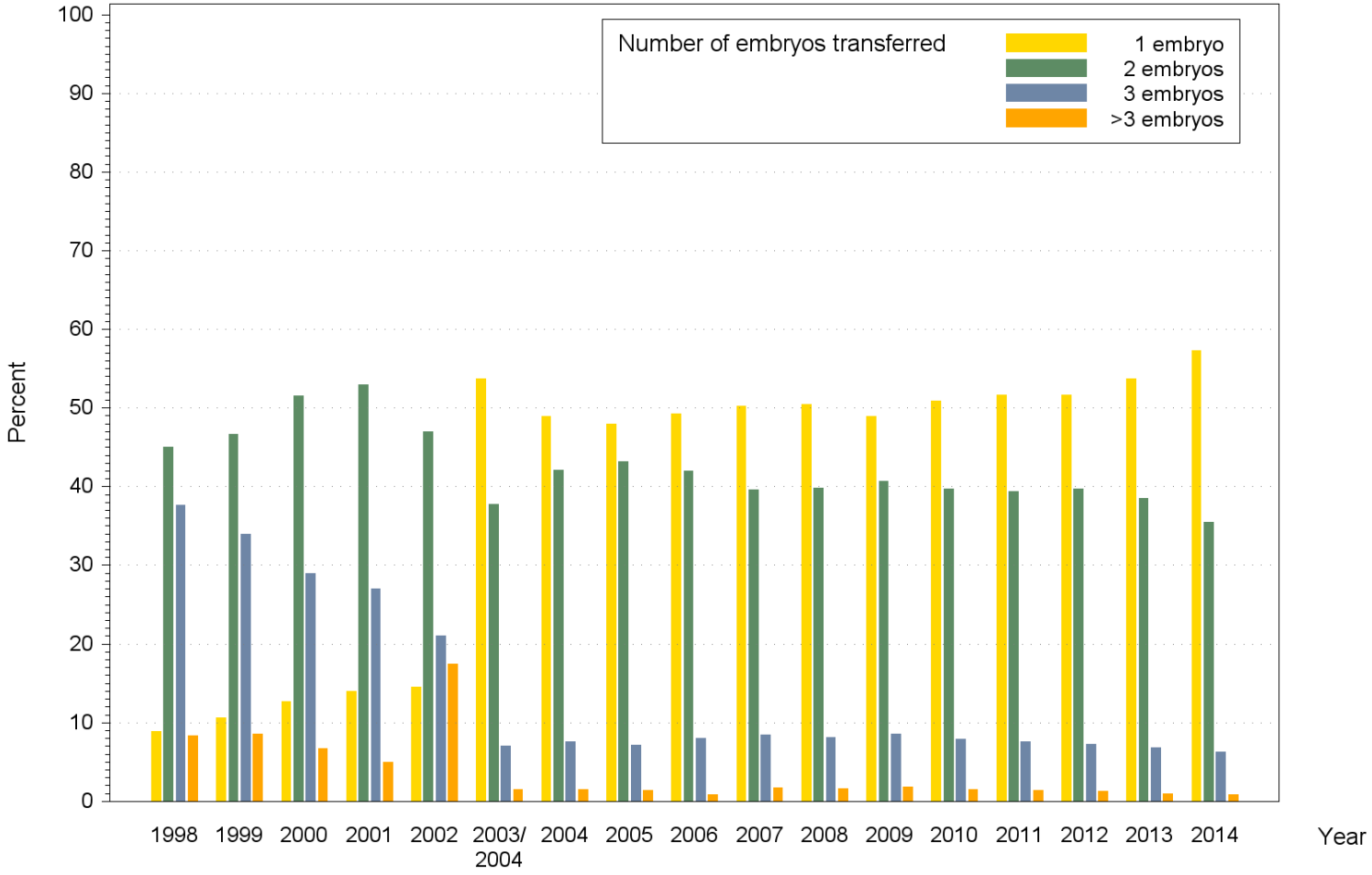
Maximal number of embryos for transfer In fresh cycles	First cycle	Second cycle	Third-sixth cycle
<36 years	1	1 (2) #	2
≥36 and <40 years	2	2	3
≥40 and <43 years	No limit	No limit	No limit

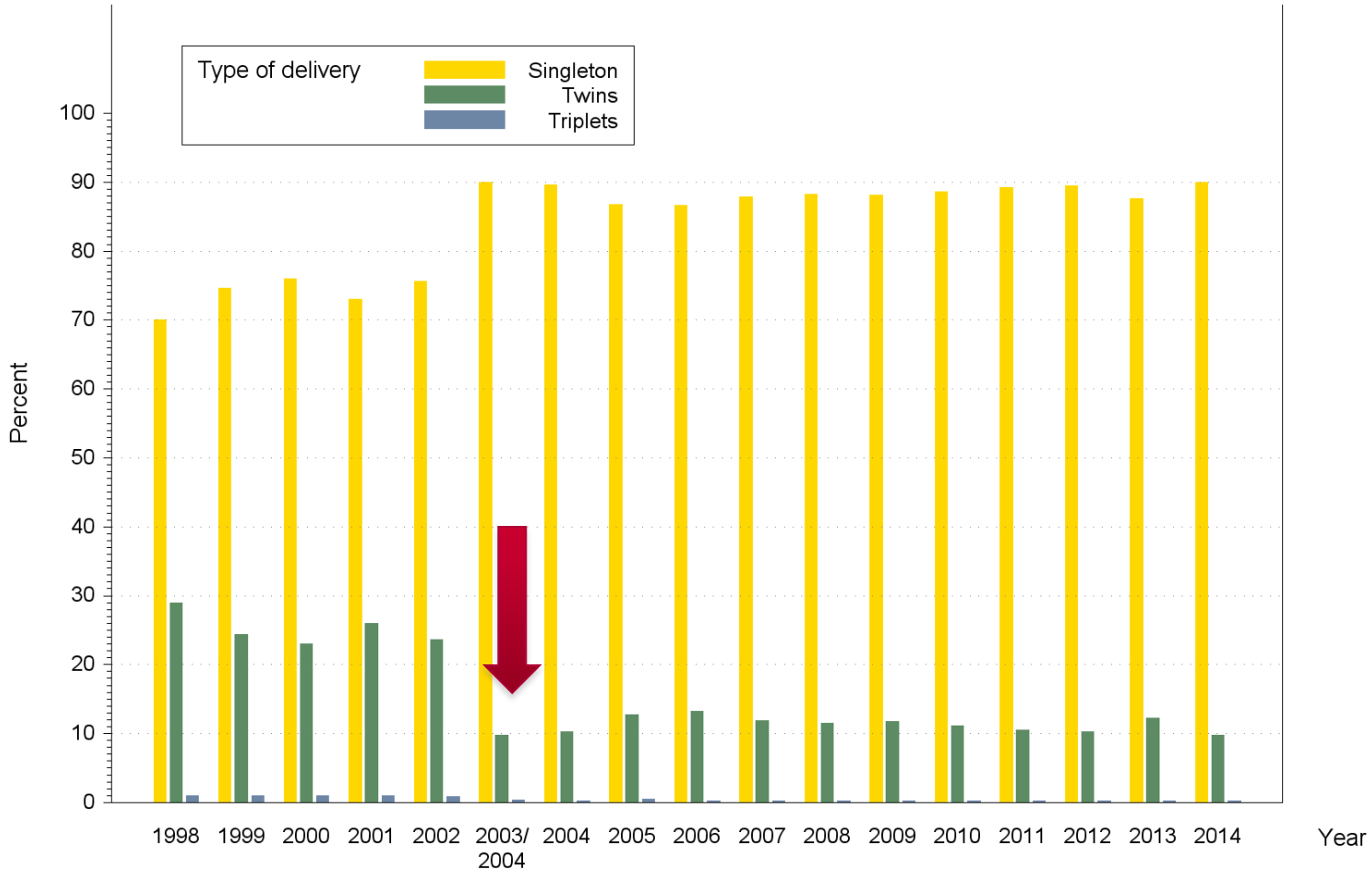
#Depending on embryo quality

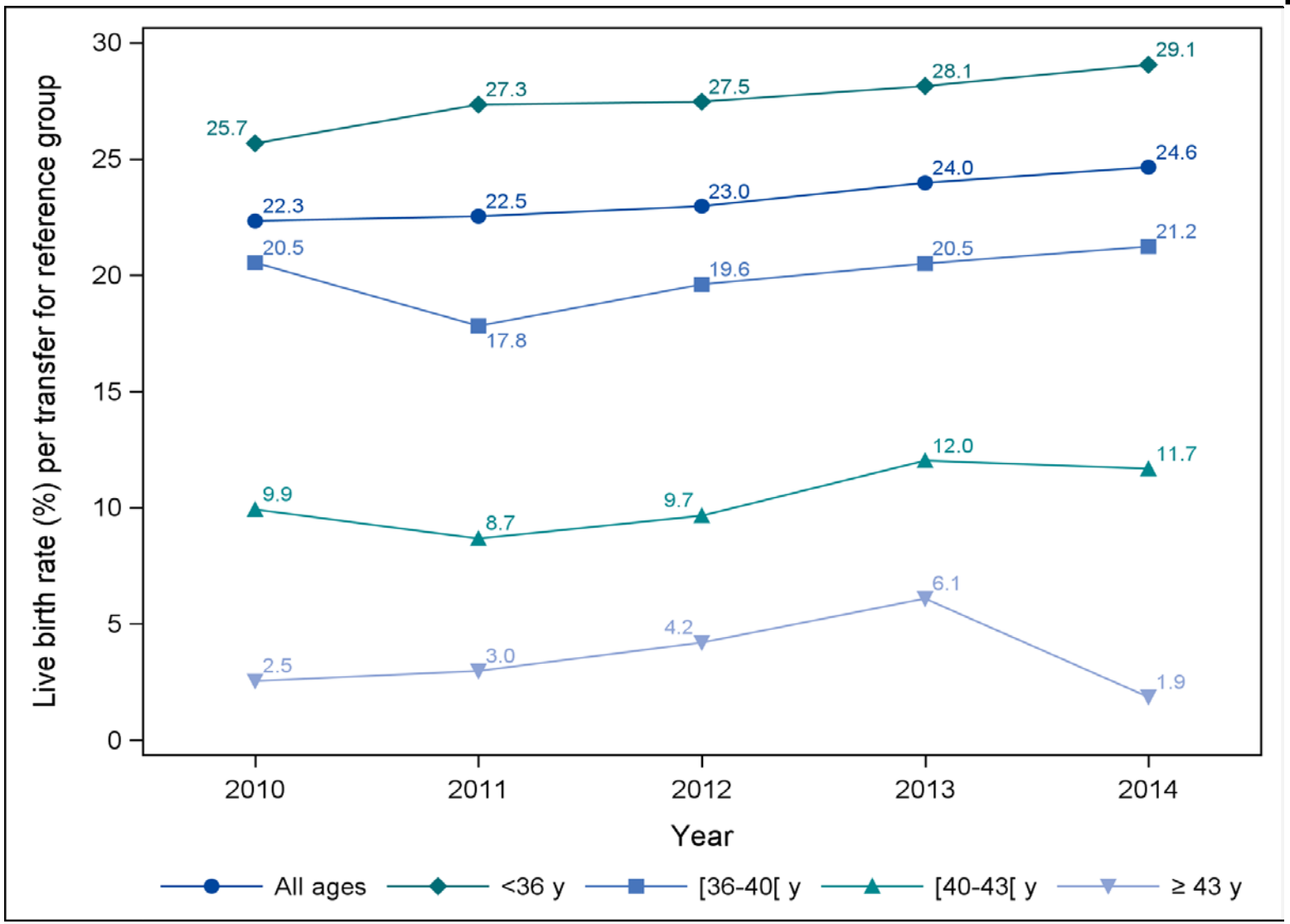
° In frozen thawed cycles, a maximum of two embryos for transfer is allowed, regardless the age of the woman.



Note: Cancelled cycles are not included in the figure.


Number of embryos transferred
1 embryo
2 embryos
3 embryos
>3 embryos
Percent
100
90
80
70
60
50
40
30
20
10
0
1998
1999
2000
2001
2002
2003/
2004
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year


Type of delivery
Singleton
Twins
Triplets
Percent
100
90
80
70
60
50
40
30
20
10
0
1998
1999
2000
2001
2002
2003/
2004
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year


Live birth rate (%) per transfer for reference group
30
25
20
15
10
5
0
2010
2011
2012
2013
2014
Year
25.7
27.3
27.5
28.1
29.1
22.3
22.5
23.0
24.0
24.6
20.5
17.8
19.6
20.5
21.2
9.9
8.7
9.7
12.0
11.7
2.5
3.0
4.2
6.1
1.9
All ages
<36 y
[36-40[y
[40-43[y
≥ 43 y

Cumulative live birth rates since the reduction in the number of transferred embryos

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Human Reproduction, Vol.31, No.1 pp. 93–99, 2016
Advanced Access publication on November 3, 2015 doi:10.1093/humrep/dev270

human reproduction ORIGINAL ARTICLE *Infertility*

How do cumulative live birth rates and cumulative multiple live birth rates over complete courses of assisted reproductive technology treatment per woman compare among registries?

D. De Neubourg[1,*], K. Bogaerts[2], C. Blockeel[3], T. Coetsier[4], A. Delvigne[5], F. Devreker[6], M. Dubois[7], N. Gillain[8], S. Gordts[9], and C. Wyns[10]

What is already known?

- Reduction in the number of embryos for transfer leads to a reduction in the multiple live birth rate.
- Live birth rate per cycle remained stable for the whole IVF patient population.

➢ per cycle analysis

Does this strategy affect the chances for the individual patient?

-> Calculation of the cumulative live birth rate and cumulative multiple live birth rate (per patient)

- Retrospective cohort
- All patients with a Belgian insurance number who started a first fresh IVF cycle
- Between 1 July 2009 until 31 December 2011
- Follow up until 31 December 2012
- Registration by Belrap (Belgian registry for Assisted procreation)
- Maximum of 6 fresh cycles with corresponding frozen cycles.

Patients

- Female age <43 years
- Cycles with own oocytes
- Non-cancelled cycles (fresh and frozen-thawed)
- Exclusion: PGD cycles, cycles after a live birth, more than 6 fresh IVF cycles

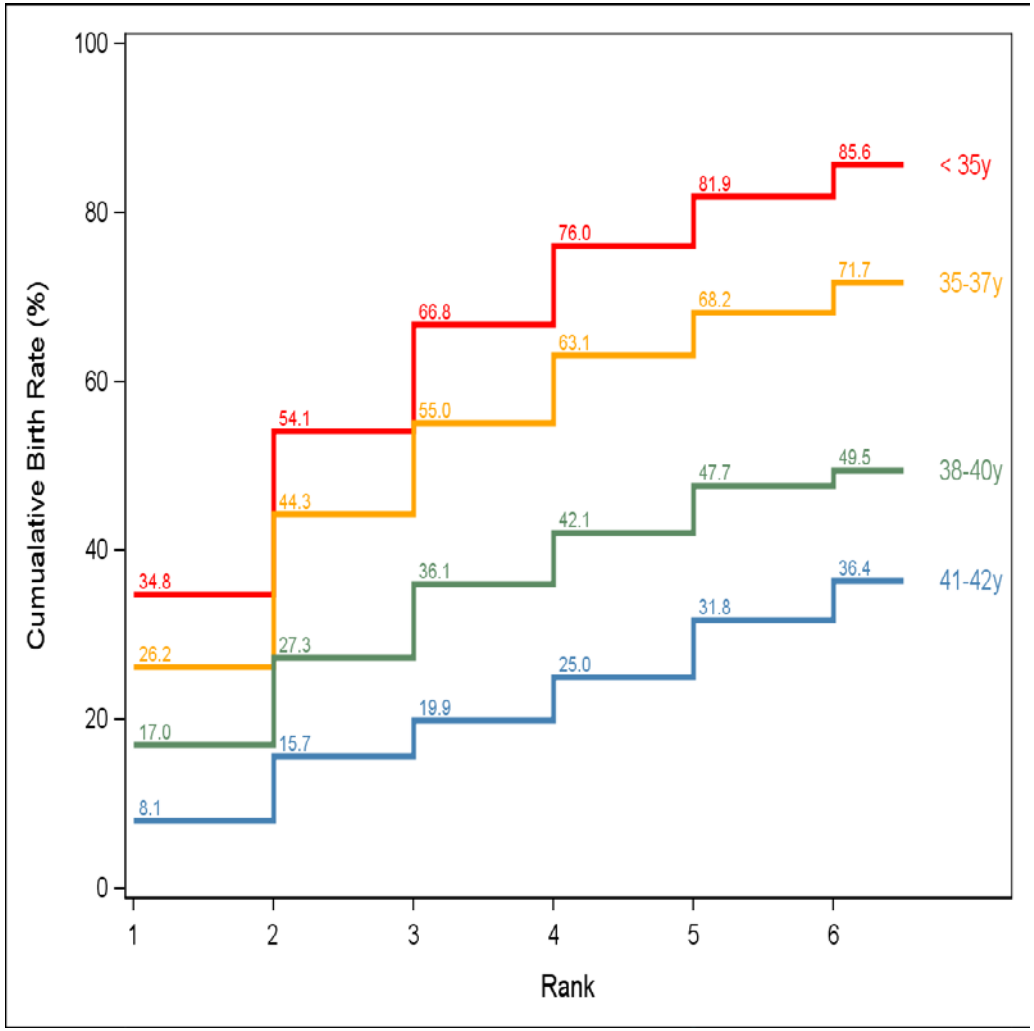
➢ 12 869 patients and 38 008 cycles (fresh and frozen-thawed).

➢ Age categories: <35; 35-37; 38-40; 41-42 years

Method of analysis

- ***Conservative estimates*** of cumulative live birth assumed that patients who did not return for treatment had no chance of achieving an ART related live birth.
- ***Optimal estimates*** assumed that women discontinuing treatment would have the same chance of achieving a live birth as those continuing treatment.

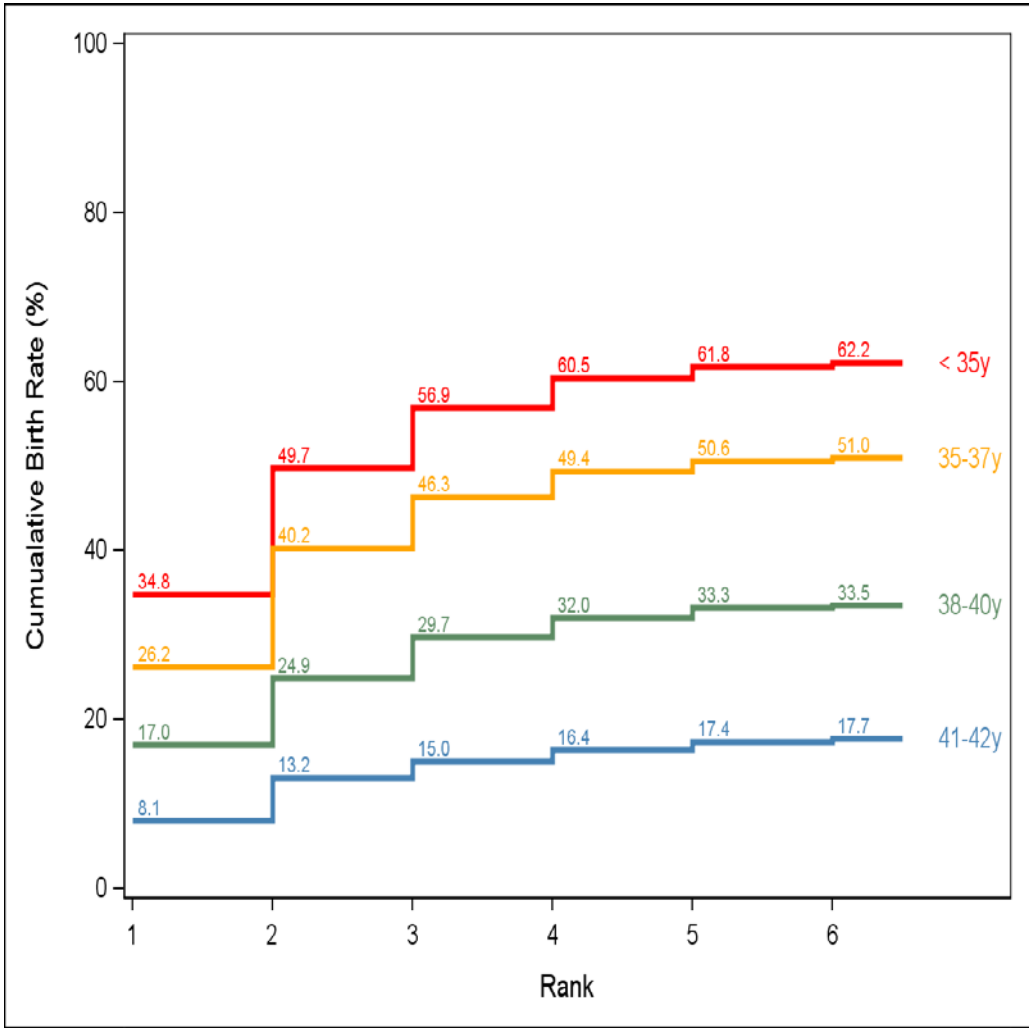
Cumulative birth rate by age group: For each course of treatment the results of fresh and frozen-thawed embryo transfer cycles following an oocyte recovery are included**. Optimal estimate.**



Cumulative multiple LBR = 8%

De Neubourg et al., Hum Reprod 2016

Cumulative birth rate by age group: For each course of treatment the results of fresh and frozen-thawed embryo transfer cycles following an oocyte recovery are included**. Conservative estimate.**



Cumulative multiple LBR = 5%

De Neubourg et al., Hum Reprod 2016

Two types of analysis

- ***"European way":*** For each course of treatment the results of fresh and frozen-thawed embryo transfer cycles following an oocyte recovery are included ("cryo-augmentation" effect).
- ***"American way":*** all embryo transfers (fresh and frozen-thawed) are included in chronological order.

Cumulative live birth rate (all ages): For each course of treatment the results of fresh and frozen-thawed embryo transfer cycles following an oocyte recovery are included.

European way	Fresh (oocyte recovery) Cycle					
	1	2	3	4	5	6
Number of women	12869	6915	3783	1984	932	408
Number of live births	3804	1714	824	410	164	51
Conditional LBR (%)	29.6	24.8	21.8	20.7	17.6	12.5
Conservative CLBR (%)	29.6	42.9	49.3	52.5	53.7	54.1
SE conservative CLBR (%)	0.4	0.44	0.44	0.44	0.44	0.44
Optimal CLBR (%)	29.6	47	58.6	67.1	72.9	76.3
SE optimal CLBR (%)	0.4	0.47	0.51	0.56	0.61	0.7
Withdrawal (%)		23.7	27.3	33	40.8	46.9

Cumulative live birth rate (all ages): all embryo transfers (fresh and frozen-thawed) in chronological order

American Way	Embryo transfer cycle						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Number of women	12869	8725	6124	4108	2693	1657	869
Number of live births	2750	1412	1028	663	494	280	175
Conditional LBR (%)	21.4	16.2	16.8	16.1	18.3	16.9	20.1
Conservative CLBR (%)	21.4	32.3	40.3	45.5	49.3	51.5	**52.9**
SE conservative CLBR (%)	0.36	0.41	0.43	0.44	0.44	0.44	0.44
Optimal CLBR (%)	21.4	34.1	45.2	54	62.4	68.8	**75.1**
SE optimal CLBR (%)	0.36	0.43	0.48	0.51	0.54	0.57	0.62
Withdrawal (%)		13.8	16.3	19.4	21.8	24.6	36.9
Mean (SD) number of embryos transferred	1.2 (0.45)	1.6 (0.57)	1.7 (0.59)	1.8 (0.63)	1.8 (0.70)	1.8 (0.66)	1.8 (0.62)

Comparison with SART data

(Luke et al., NEJM, 2012)

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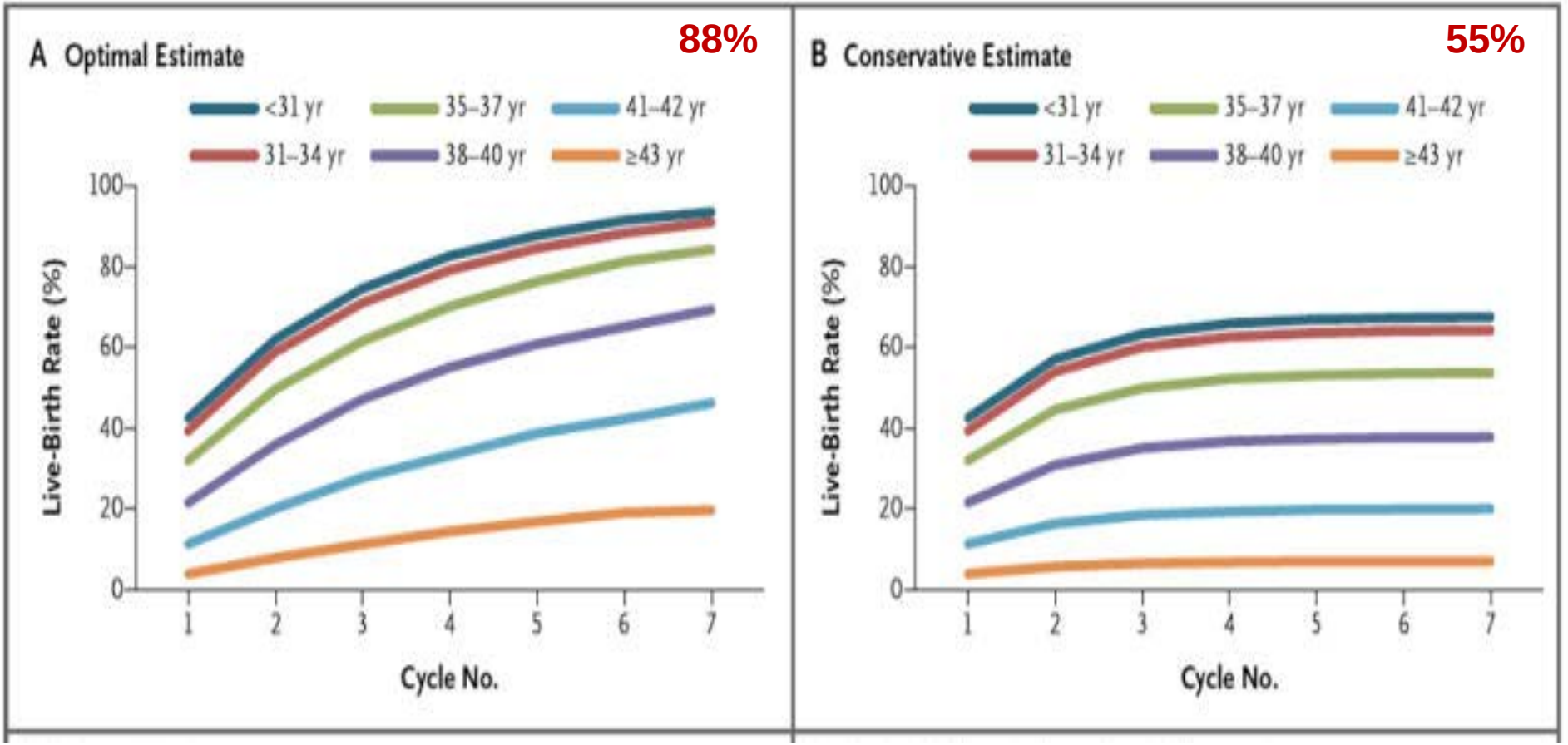
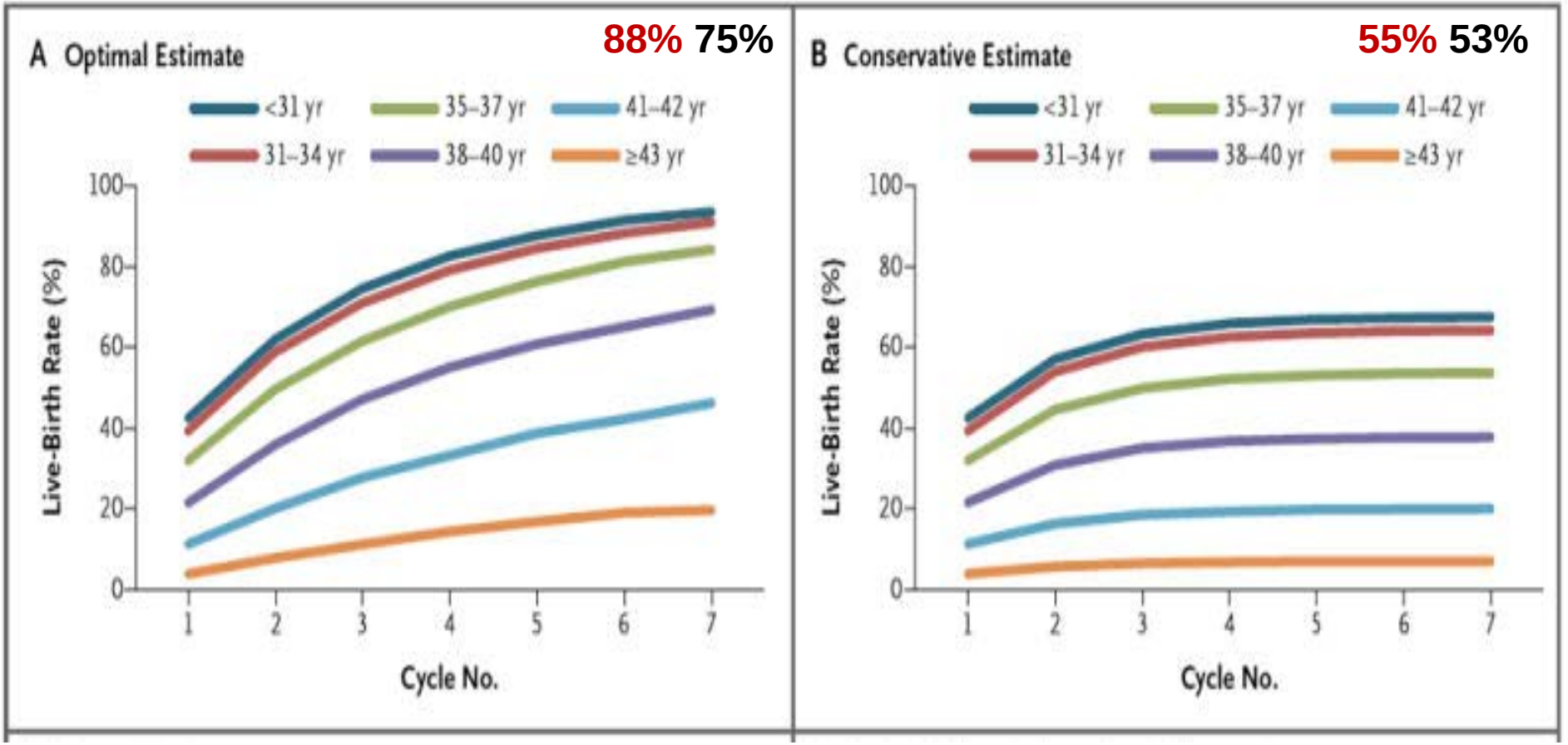

A Optimal Estimate
88%
<31 yr
31–34 yr
35–37 yr
38–40 yr
41–42 yr
≥43 yr
Live-Birth Rate (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
Cycle No.
B Conservative Estimate
55%
<31 yr
31–34 yr
35–37 yr
38–40 yr
41–42 yr
≥43 yr
Live-Birth Rate (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
Cycle No.

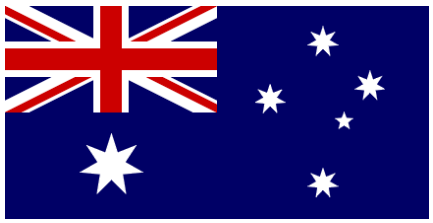
multiple LBR per ET = 28% in 2011



P<0.0001

Comparison with Australian-New Zealand ART data

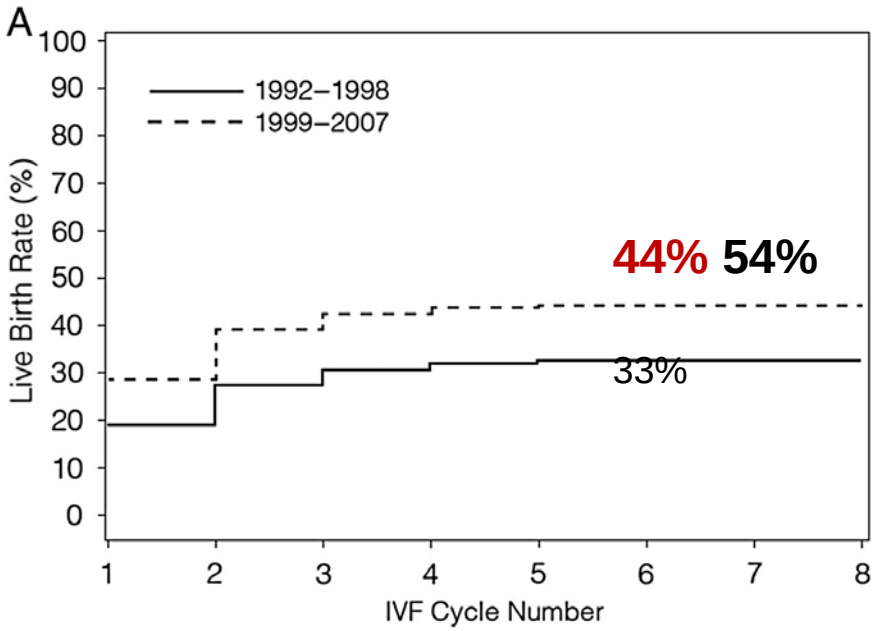
- Comparison with the Australian – New Zealand ART data as registered by the National Perinatal Epidemiology and Statistics Unit (NPESU, 2011)
- Analysis of patients that started their first autologous fresh ART treatment cycle during 2009-2011.
- After 7 consecutive cycles the cumulative live birth rate was **41.1%** which was significantly lower ($p<0.0001$).
- Multiple LBR= 10.0% in 2007 en 6.9% in 2011.



Comparison with HFEA data

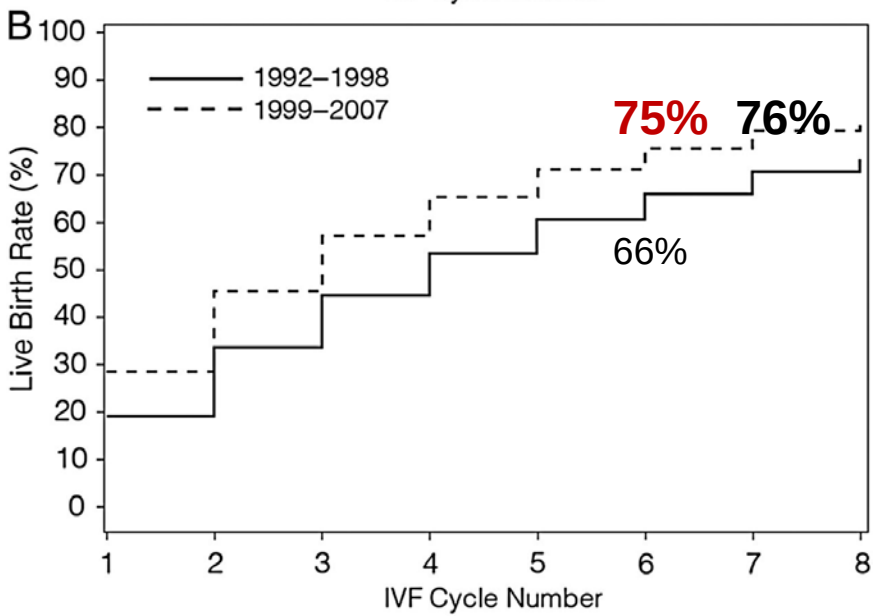
(McLernon et al., Hum Reprod , 2016)

Cumulative live birth rate For each course of treatment the results of fresh and frozen-thawed embryo transfer cycles following an oocyte recovery are included.



Conservative estimate

McLernon et al.
Hum. Reprod. 2016



Optimal estimate

Cumulative multiple LBR = 26%!

Comparison with UK data 2003-2010

(Smith A et al., JAMA, 2015)

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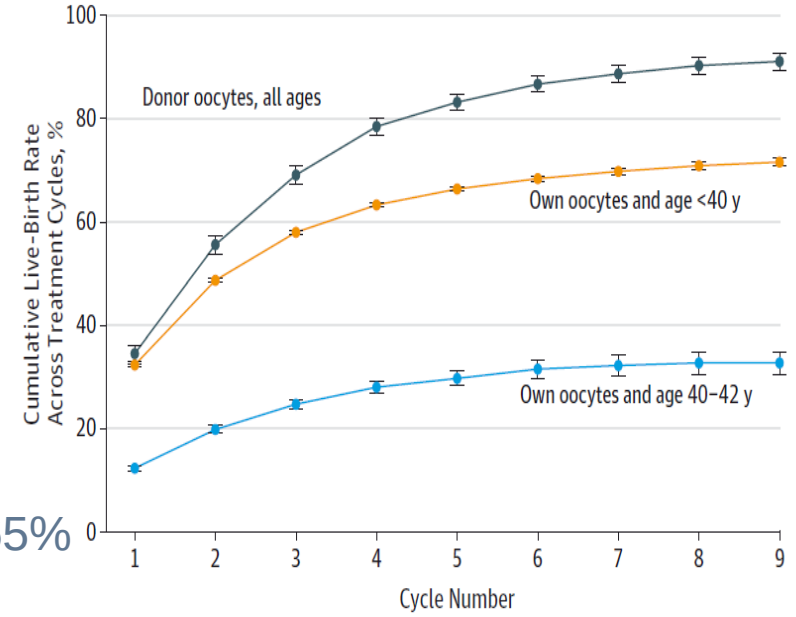
Figure 2. Cumulative Live-Birth Rate Across All Initiated IVF Cycles by Age and Oocyte Source



No. of women									
Donor oocytes, all ages	3587	1636	939	554	287	126	53	27	8
Own oocytes and age <40 y	133379	53568	19719	6641	2357	882	335	131	51
Own oocytes and age 40–42 y	15561	6671	2579	884	301	130	60	36	20
Own oocytes and age >42 y	4420	1578	509	160	67	24	10	5	4

Optimal estimate 78%
Conservative estimate 47%
Prognostic-adjusted estimate 65%

How does a reduction in the multiple pregancy rate affect ART related costs?

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How did this affect ART related costs?

- Only patients that had their complete ART treatment, pregnancy follow up and delivery in UZ Leuven in order to obtain all hospital related costs.
- All costs for the mother (ART related, pregnancy & delivery) and child untill the age of two.
- All invoices related to hospital costs.

Peeraer et al., RBM online, accepted

Projected cost reduction per 100 patients since 2003

	Total cost €		**Total Cost reduction (€)**	**Total Cost reduction (%)**
100 patients before Belgian legislation: 76 singleton pregnancies; 76 singletons 24 twin pregnancies, 48 twins	2.399.344		306.372	12.8%
100 patients after Belgian legislation: 88 singleton pregnancies, 88 singletons 12 twin pregnancies; 24 twins	2.092.972			
	Total cost per mother €	Cost per mother (€)	Total Cost reduction (€)	Total Cost reduction (%)
100 patients before Belgian legislation: 76 singleton pregnancies 24 twin pregnancies	1.308.196	13.082	38.148	3%
100 patients after Belgian legislation: 88 singleton pregnancies 12 twin pregnancies	1.270.048	12.700		
	Total cost per child €	Cost per child (€)	Total Cost reduction (€)	Total Cost reduction (%)
100 patients before Belgian legislation: 76 singletons 48 twins	1.091.124	8799	268.212	
100 patients after Belgian legislation: 88 singletons 24 twins	822.912	6745		

Projected cost reduction per 100 patients since 2003

	Total cost (€)		Total Cost reduction (€)	Total Cost reduction (%)
100 patients before Belgian legislation: 76 singleton pregnancies; 76 singletons 24 twin pregnancies, 48 twins	2.399.344		306.372	12.8%
100 patients after Belgian legislation: 88 singleton pregnancies, 88 singletons 12 twin pregnancies; 24 twins	2.092.972			

Peeraer et al., RBM online, accepted

The Belgian Model

Regulation

- ***Safety***
  50% reduction in twins
- ***Effectiveness***
  CLBR unaffected

Reimbursement

- ***Efficiency***
  13% reduction in costs

Increased access to fertility treatment

De Neubourg et al., BMJ 2014

Conclusion

- Since the introduction of the single embryo transfer strategy in 2003, cumulative live birth rates remain high when compared to other registries and publications
- AND with a low cumulative multiple live birth rate !
- The “Belgian model” coupling reimbursement of the majority of ART related costs to a reduction in the number of embryos transferred did and still does work out well.