

## Prevention of multiple pregnancies after assisted reproduction: the Belgian project

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### Abstract

An increased incidence of maternal, perinatal and childhood morbidity and mortality has been described due to the epidemic of iatrogenic multiple births as a result of infertility treatment. The result is a much higher healthcare cost of infertility therapy which automatically will lead to social and political concern.

Single embryo transfer in selected cases seems to be the best option in reducing the number of multiples after IVF/ICSI. The Belgian project in which reimbursement of ART-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction and taking into account the age and cycle number of the patient, is a good example of forward-looking health economics. The twin pregnancy rate has dropped to 10% and triplet pregnancies almost disappeared.

Considering non-IVF assisted reproductive technologies: a low multiple pregnancy rate of less than 5% is noted in Belgium for IUI procedures with homologous and donor semen. This can easily be explained: in almost 80% of IUI cycles no ovarian stimulation (natural cycle) or clomiphene citrate has been used. When gonadotrophines are used, our aim is to support the growth of one or two follicles, so avoiding the high risk for multiples.

**Key words:** Cost-effectiveness, IUI, infertility treatment, IVF, multiple pregnancies, policy, reimbursement.

### Introduction

The major side effect of assisted reproductive technology is undoubtedly the high incidence of multiple pregnancies, responsible for a substantial part of the costs and suffering. By the end of the 90s assisted reproduction (ART) accounted for 0.08-0.16% of the total health care costs in the Nordic countries (Granberg et al., 1998) while in the USA expenses for infertility, including IVF, were responsible for 0.4-0.8% of these costs (Stovall et al., 1999; Griffin and Panak, 1998).

In terms of absolute figures and because of their higher incidence, twin pregnancies outweigh by far the effect of high-order multiple pregnancies. The most efficient way to reduce the costs and the distress experienced by couples in ART is the prevention of multiple pregnancies, not only the high-order multiples, but even more important the reduction of twin pregnancies. For IVF-ICSI the improving insights in embryo quality assessments,

followed by single embryo transfer could be the method of choice, especially in the good prognosis group.

### Avoiding multiple pregnancies: why?

In most developing countries, 30% to 50% of all twin pregnancies are linked to infertility treatment. In 2000 and 2001 the perinatal mortality (PNM) of singletons in Flanders was 6.7 per 1000 births, in twins the mortality rate rose to 26.9 per 1000 births, while higher order multiples even reached PNM rates as high as 68.2 per 1000 deliveries (Cammu et al., 2002). Preterm delivery occurs in more than 80% of triplet and 100% in quadruplet pregnancies. Very low birth weight infants are derived 9 times and 29 times more often in twin and triplet pregnancies respectively. This leads to an increased rate of neonatal care admission, more days of ventilatory support and a higher frequency of intraventricular haemorrhage and necrotizing

enterocolitis. Long-term infant morbidity is reflected in mental and physical disabilities. At least one handicapped child is found in 7.4%, 21.6% and 50% for twin, triplet and quadruplet pregnancies respectively.

Maternal complications include a significant increase in anaemia, gestational diabetes (10%), hypertension, pre-eclampsia (30%) and post-partum haemorrhage (10%). Dystocia and a high caesarean section-rate will contribute to the excess maternal morbidity. All these complications lead to a dramatic rise in days of hospitalization and the subsequent increased financial costs.

On the other hand, pressure to achieve higher pregnancy rates in infertility treatment have resulted in an unacceptable high multiple pregnancy rate in many countries. In the United States, multiple births occur after more than 35% of IVF cycles (Katz et al., 2002; Sunderam et al., 2013).

Interesting but most frightening was the observation that, in 1998, of all infants born after IVF and/or ICSI only 57.3% were born as singletons. 37.1% were born as twins and 5.6% as triplets or quadruplet.

Looking at these data, the prevention of multiple gestations became the most important challenge, not only to reduce the economic costs of infertility-related services but even more important to improve perinatal health.

## The Belgian project

### For IVF/ICSI

In Belgium there has been a steady decline in the number of embryos transferred since 1997. The proportion of deliveries of multiples after ART has also decreased from 34% in 1992 to 24% in 2000.

The introduction of single embryo transfer (SET) (Gerris et al., 1999; De Sutter et al., 2002) has certainly accelerated this evolution. SET was performed in 14% of all transfers in Belgium in 2001 and this figure was increasing each year. Surprisingly, this strategy did not affect the overall national results. The ongoing pregnancy rate per transfer has always fluctuated around 20% for the last ten years and remained 22% in 2001, although less embryos were transferred.

Until 2002, about 75% of the medical costs of assisted reproductive technologies were reimbursed by the government. These costs included the medication used, the visits and the costs for monitoring (ultrasonography, hormonal). There was no reimbursement for the laboratory costs at all, neither for IVF-ICSI or IUI.

In 2001 the Belgian government decided to change the reimbursement policy in IVF-related procedures. The first objective was to increase accessibility to infertility treatment. It was mentioned from the start that financial resources were limited and as a result, a certain inventiveness was called for.

Therefore, the Belgian College of Reproductive Medicine (BCRM), in cooperation with all licensed IVF centres, agreed on a proposal to the government in which reimbursement of IVF and ICSI treatment cycles would be linked to a 50% reduction of twin pregnancies, subsequently minimizing the risks for high order multiple pregnancies to almost zero. This proposal was based on a reduction of embryos transferred after ART, considering the possible influence of female age and cycle number on the incidence of multiple pregnancies (Table I). Following a study of the direct laboratory costs for IVF +/- ICSI, it was concluded that 1.250 Euro would be a fair reimbursement for the laboratory

**Table I.** — Reducing the multiple pregnancy rate in IVF-related procedures using fresh embryos: the Belgian strategy.

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

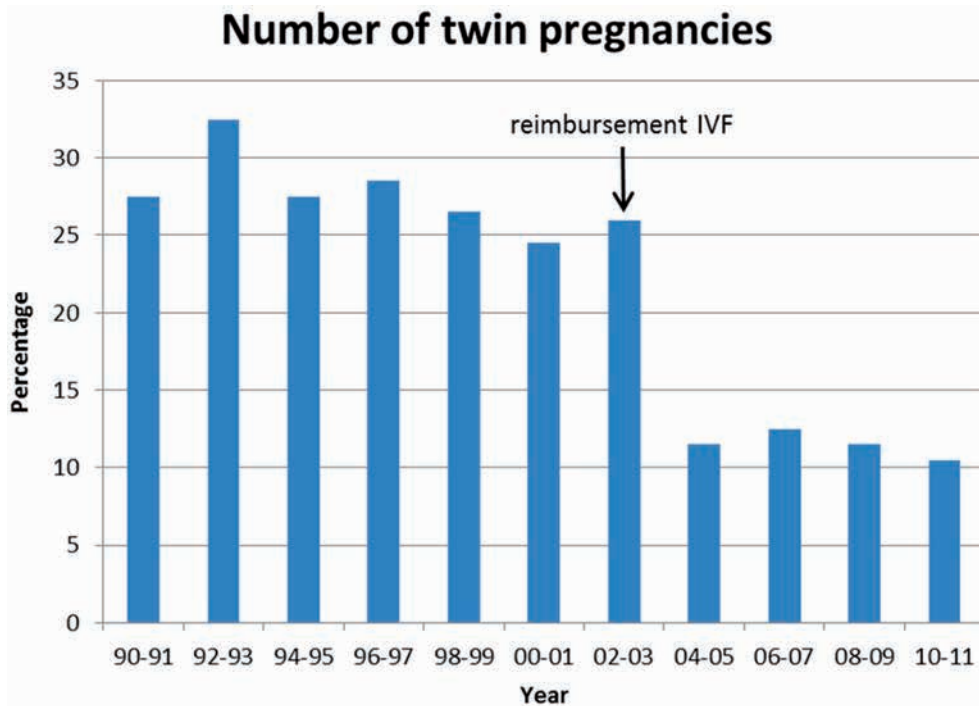


Fig. 1. — Effect of the Belgian reimbursement policy on the number of twin pregnancies.

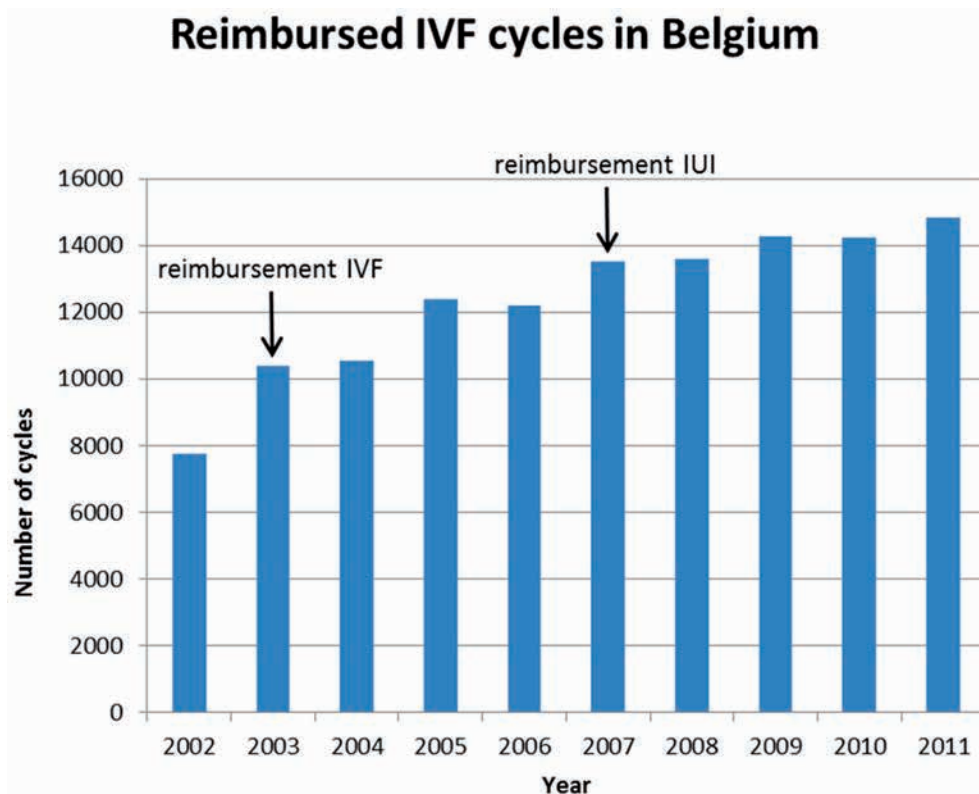


Fig. 2. — Influence of the Belgian reimbursement policy on the number of IVF/ICSI cycles.

costs associated to IVF/ICSI at that moment. The government decided to reimburse 6 IVF/ICSI cycles in a lifetime, provided the suggested strategy dropped from 26.5% in 2002 and 10.5% in 2011 (Ombelet et al., 2005, Fig. 1).

*For IUI*

It was to be expected that the number of IVF cycles would increase due to the reimbursement policy. The reimbursed IVF cycles almost doubled from

**Table II.** — Live birth rate (LBR) and multiple pregnancy rate in Belgium (BELRAP data) and Europe (ESHRE data). (AID = artificial insemination with donor semen, AIH = artificial insemination with partner's semen).

	Number of cycles	LBR/cycle	Twin	Triplet
<b>BELRAP 2010-2011</b>				
KID	11031	8,60%		
AIH	19463	6,80%		
Total	30494	7,50%	3,30%	0,01%
<b>ESHRE 2010</b>				
KID	38124	13,80%	7,90%	0,20%
AIH	176512	8,90%	9,30%	0,50%
Total	214636	9,30%	8,90%	0,40%

7759 in 2002 to 14833 in 2011 (Fig. 2). Therefore, the government decided to reimburse IUI treatment as well, in order to avoid too many unnecessary IVF procedures. Due to the fact that in Belgium more than 80% of IUI cycles are performed in a natural cycle or after the use of clomiphene citrate, the live birth rate per IUI attempt but is low compared to other European countries, the advantage is that the twin pregnancy rate is also extremely low, namely 3.3% twins and 0.1% triplets compared to 9.3% twins and 0.5% triplets in 2010 in Europe (BELRAP rapport 2010-2011, Kupka et al., 2014; Table II).

## Conclusion

The reduction of embryos transferred after IVF and/or ICSI resulted in a higher proportion of singletons. The Belgian project in which reimbursement of laboratory activities is linked to a limited number of embryos transferred in order to reduce the twin pregnancy rate by 50% and the high order multiplets to almost zero is also unique from a health-economical point of view.

The IUI multiple pregnancy rate in Belgium remains very low due to the use of natural cycle IUI or mild ovarian stimulation protocols with clomiphene citrate and/or low-dose urinary gonadotrophins or recombinant FSH.

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