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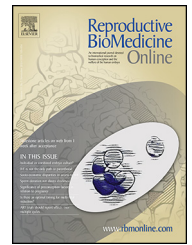
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ARTICLE

Seven out of 10 couples treated by IVF achieve parenthood following either treatment, natural conception or adoption




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Abstract The aim of this study was to explore the achievement of parenthood 8 years after starting IVF, considering multiple pathways to parenthood during and after IVF treatment. Medical data on 6507 couples who began IVF between 2000 and 2002 were obtained from the databases of eight French IVF centres. Information on long-term outcome was available for participants in the 2008–2010 postal survey. Multiple imputation methods were used to account for missing data. Eight years after starting IVF, 71% (95% CI 69 to 74) of treated couples had a child. This included 41% live births after IVF in the IVF centre, 7% live births after another treatment or after IVF in another centre, 12% live births after spontaneous conception and 11% adoptions. This study provides a longitudinal overview of paths to parenthood among couples successfully and unsuccessfully treated by IVF. These results should give hope to infertile couples as seven out of 10 couples finally became parents. However, IVF is not the only path to parenthood, and couples should be informed of the other possible avenues. 

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KEYWORDS: follow-up studies, in vitro fertilization, multiple imputation, parenthood

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Introduction

Infertility is estimated to affect one couple out of four (Slama et al., 2012), and the number of couples seeking medical help has clearly increased in recent decades (Boivin et al., 2007; Bushnik et al., 2012a). In Canada, for example, the prevalence of past-12-month infertility has tripled between 1984 and 2010 (Bushnik et al., 2012b). Assisted reproductive techniques, and especially IVF, are now widely used in developed countries (Kupka et al., 2016; Sunderam et al., 2015). The success of IVF has long been measured on the basis of pregnancy rate per one IVF cycle, but this indicator has been debated (Min et al., 2004; Pinborg et al., 2004). Several proposals have been made for considering success as delivery of healthy babies. With patient counselling in mind (Malizia et al., 2009; Moragianni and Penzias, 2010), a more relevant approach has been developed by reporting success rates in terms of cumulative live-birth rate (CLBR) per woman during her entire treatment (Gnoth et al., 2011; Maheshwari et al., 2015; Malizia et al., 2013; McLernon et al., 2016). This CLBR indicator gives a more long-term view of the chance of success by considering not just a single IVF cycle but all the IVF cycles undergone by a woman. For instance, in a recent Japanese study, the CLBR was estimated to be 38% (Bodri et al., 2014).

On completion of the various IVF cycles undertaken by couples, leaving the IVF centre childless is usually perceived as the end of any hope of parenthood. It is timely, however, to challenge such a view and to explore the long-term outcome of couples leaving an IVF centre childless. Indeed, patients often ask about their chances of conceiving naturally, i.e. without any medical help (Cahill et al., 2005), and some studies have shown that spontaneous pregnancy can occur after unsuccessful IVF treatment (Cahill et al., 2005; Osmanagaoglu et al., 2002). Moreover, some couples shift their parental project to adoption as another path to fulfill their desire for parenthood (Sydsjö et al., 2005). Few studies have been able to provide a full overview of these different paths to parenthood among unsuccessfully treated couples (de La Rochebrochard et al., 2009; Walschaerts et al., 2012; Wischmann et al., 2012). Indeed, studies on the long-term outcome of couples treated by IVF require follow-up over several years. Such a long-term approach is hampered by a high risk of loss to follow-up, even when costly longitudinal protocols are used (Chen et al., 2011; Cotter et al., 2005; Robinson et al., 2015). These methodological issues may explain the sparse results published so far.

The aim of this study was to provide a long-term overview of the different paths to parenthood 8 years after starting IVF. It considers births achieved after several cycles of IVF treatment in the centre (the CLBR), births achieved after other subsequent treatments, as well as spontaneous births obtained without medical assistance. To develop a full perspective of paths to parenthood, adoption was also taken into account as another way for couples to fulfill their desire to become parents.

Materials and methods

Population and sources of data

DAIFI (the French acronym for outcome after IVF) is a retrospective cohort (Troude et al., 2012). It is an exhaustive

database of all 6507 couples who began IVF between 2000 and 2002 in eight French IVF centres (among the 93 IVF centres in metropolitan France). This study received approval from the French Data Protection Authority on 9 September 2005 (authorization number 05-1334).

Data collection included two complementary sources: medical data obtained from the IVF centres and information based on a postal questionnaire. In this paper, information from the postal questionnaire was used to explore long-term outcome among unsuccessfully treated couples. A full presentation of the postal survey is available elsewhere, including a detailed analysis of participation (Troude et al., 2012).

Medical data collected in the whole cohort

Medical data were obtained from the IVF centre databases. All IVF treatments carried out in the centres between 2000 and 2007 were exhaustively recorded for the 6507 couples of the cohort. Medical data included sterility assessments for the couple (age, origin, type and duration of infertility), information on each IVF treatment carried out in the centre (number of oocytes retrieved, number of embryos obtained, number of embryos transferred, pregnancy after fresh or frozen embryo transfer) and on the outcome of any ensuing pregnancies. On the basis of these medical data, two groups were identified among the 6507 couples of the cohort: 2691 couples successfully treated in the centre and leaving it with a child, and 3816 couples unsuccessfully treated in the centre and leaving it childless (Figure 1).

Long-term outcome data among unsuccessfully treated couples

Long-term outcome was explored in the postal questionnaire carried out between 2008 and 2010. Different steps toward parenthood were considered: live birth after another treatment at a later date (further IVF treatment in another centre or another treatment such as sperm insemination) and live birth after spontaneous conception. As well as these paths to 'biological' parenthood, the study also explored adoptive parenthood as an alternative path for the couple to fulfill their desire to have a child.

In the postal survey, to increase chances of contact, every effort was made to obtain updated validated mailing addresses through the central hospital billing department and through the French postal system. Of the 3816 couples unsuccessfully treated in the IVF centre, 2274 couples (60%) were contacted in the postal survey 8 years after registration in the IVF centre (Figure 1).

To increase the chance of response among contacted couples, effective 'response-enhancement' strategies were used (Edwards et al., 2002; MacDonald et al., 2009). In particular, a relatively short, colour-printed questionnaire designed to be user-friendly was distributed to participants, and stamped-addressed envelopes were provided. If necessary, a reminder was sent, including a second copy of the questionnaire, requesting an explanation of non-participation. Of the 2274 couples contacted by mail, 1100 couples (48%) returned a completed questionnaire (Figure 1). This response

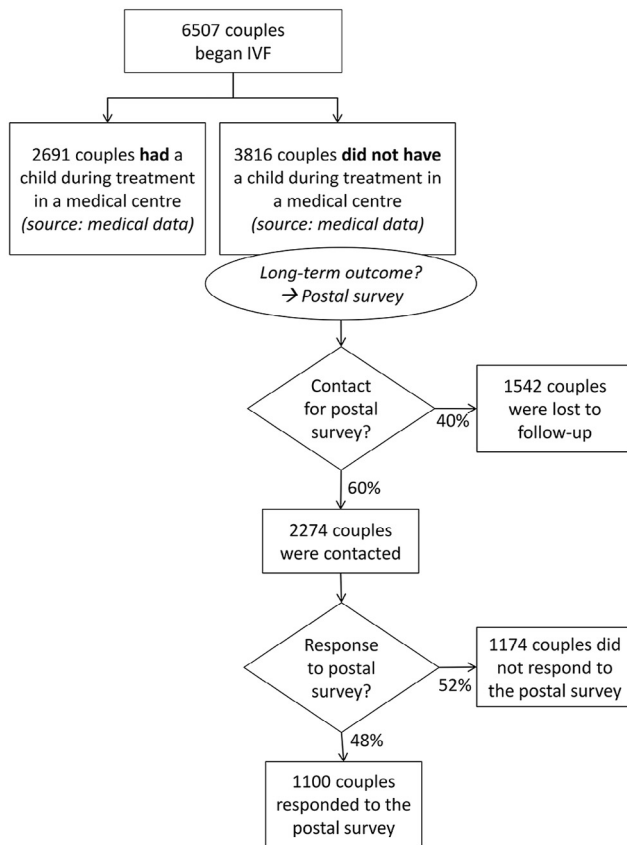


Figure 1 Couples included in the study.

rate was moderate but consistent with the expected response rate in patient surveys considering that, in this study, patients were interviewed about past events (Asch et al., 1997). Because of this non-participation, classic epidemiological statistical tools did not seem appropriate for analysing the data from the postal survey, and cutting edge statistical methods were, therefore, used.

Strategy of analysis

The postal survey was analysed on the basis of post-survey adjustment methods developed to produce unbiased results for datasets affected by non-participation (Donders et al., 2006; Graham, 2009; Groves, 2006; Harel and Boyko, 2013; He, 2010; Little and Rubin, 1987; MacDonald et al., 2009; Ranstam et al., 2012; Schafer and Graham, 2002; Wang and Hall, 2010). In this analysis, non-participants in the postal survey were included in the estimation of long-term parenthood achievement using multiple imputation by chained equations (Azur et al., 2011; Royston and White, 2011; van Buuren et al., 1999).

Values of non-participants were imputed on the basis of their medical characteristics. The model of imputation relies on a multivariate logistic regression describing medical factors associated with parenthood achievement ($P < 0.20$) among unsuccessfully treated couples who participated in the postal survey. To account for uncertainty in the imputed values, imputation was repeated several times for each participant

(multiple imputation). To test the stability of our results obtained through multiple imputation strategy, a sensitivity analysis was conducted. A supplementary auxiliary parameter was introduced in the model: a deprivation score (the Carstairs index) as an indicator of couples' socioeconomic level. This index was based on the characteristics of the couple's area of residence collected in the 1999 French census and available for 88% of the study sample (3373/3816).

The confidence interval of the overall parenthood achievement rate was calculated using an estimation of the standard error carried out by the delta method (Buehler, 1957). All statistical analyses and imputations were conducted using STATA/SE 12.0 (Stata Press, College Station, TX, USA), particularly the *mi impute chained* command of Stata software.

Results

Characteristics of the study population and CLBR

In the whole cohort ($n = 6507$), the median age of the women at first oocyte retrieval was 33 years (quartiles Q1–Q3 [30–37]) and the median age of the men was 35 years (Q1–Q3 [31–39]) (Table 1). For one-third of couples (2108/6470), infertility was caused by male factor, for 36% (2353/6470) a female factor, mixed factors for 18% (1176/6470) and unexplained for 13% (833/6470) of couples. The median number of IVF

Table 1 Characteristics of couples and outcome of IVF treatment in the IVF centre ($n = 6507$).

	Distribution (%)
Woman's age (years) at first IVF	
<30	24
30–34	37
35–39	28
≥40	11
Man's age (years) at first IVF	
<30	14
30–34	34
35–39	29
≥40	23
Origin of infertility	
Female	36
Male	33
Couple	18
Unexplained	13
Year of first IVF	
2000	27
2001	38
2002	35
Number of IVF cycles during treatment	
1	42
2	27
3	16
≥4	16
Outcome of IVF treatment in the centre	
Live birth	41
No live birth	59

attempts at the IVF centre was two (Q1-Q3 [1-3]). The treatment ended successfully with a live birth for 41% (2691/6507) of the couples of the cohort. The CLBR was thus 41% (95% CI 40 to 43).

Long-term parenthood achievement after unsuccessful IVF treatment

At the end of treatment at the IVF centre, 59% (3816/6507) of treated couples remained childless. Of these unsuccessfully treated couples, 1100 participated in the postal survey (Figure 1). These unsuccessfully treated couples who participated in the survey included 561 couples who finally later succeeded in having a child (biologically or by adoption) and

539 couples who still remained childless. The characteristics of these two groups are described in Table 2, which also shows the proportion of couples who had a child (biologically or by adoption) according to the couples' characteristics. For instance, 69% (134/194) of women under 30 years later succeeded in becoming parents, whereas this percentage was 33% (44/134) for women older than 40 years.

Factors associated with long-term parenthood achievement among unsuccessfully treated couples are presented in Table 3. The probability of parenthood achievement decreased strongly with increasing age of the woman. It was also associated with year of first oocyte retrieval, outcome of the first IVF, number of IVFs and IVF centre. Using these factors in the multiple imputation model, the proportion of couples achieving parenthood (biologically or by adoption) was

Table 2 Characteristics according to long-term biological and adoptive parenthood achievement among the 1100 couples unsuccessfully treated in the IVF centre and who participated in the postal survey.

	Distribution of couples who			Proportion of couples who had a biological or adopted child (n = 1100) %
	did not have a child (n = 539) %	had a biological or adopted child (n = 561) %	P χ^2	
Woman's age (years) at first oocyte retrieval			<0.001	
<30	11	24		69
30-34	36	43		55
35-39	36	25		42
≥40	17	8		33
Year of first oocyte retrieval			<0.001	
2000	19	24		56
2001	36	43		56
2002	45	34		44
Origin of infertility			0.631	
Female	39	39		51
Male	32	29		49
Couple	18	18		52
Unexplained	11	14		55
Number of embryos obtained at first IVF			0.157	
0	15	12		45
1-2	22	20		49
3-5	35	35		51
>5	27	33		56
Outcome of first IVF ^a			0.009	
0-1 oocyte	3	2		35
≥ 2 oocytes	9	10		52
Transfer	68	63		49
Frozen	16	18		53
Pregnancy	4	8		70
Number of oocyte retrievals			0.071	
1	26	28		53
2	27	27		52
3	18	22		56
≥ 4	29	22		45
At least one embryo transferred during all IVFs in the centre			0.055	
No	9	6		41
Yes	91	94		52

^aVariable corresponding to the step at which the first IVF failed, in five categories: less than two oocytes retrieved but no transfer; two or more oocytes retrieved but no transfer; embryos transferred but no embryo frozen and no pregnancy; embryos transferred and frozen but no pregnancy; pregnancy after fresh or frozen embryo transfer which resulted in an ectopic pregnancy, spontaneous abortion or stillbirth.

Table 3 Factors associated in logistic regressions with parenthood achievement (biologically or by adoption) among the 1100 couples unsuccessfully treated in the IVF centre and who participated in the postal survey.

	n	Univariate analysis			Multivariate analysis ^a		
		OR	95% CI	P	OR	95% CI	P
Woman's age (years) at first oocyte retrieval				<0.001			<0.001
<30	134/194	1.80	1.26 to 2.58		1.96	1.35 to 2.85	
30-34	243/439	1			1		
35-39	140/333	0.59	0.44 to 0.78		0.53	0.39 to 0.72	
≥40	44/134	0.39	0.26 to 0.59		0.35	0.23 to 0.54	
Year of first oocyte retrieval				<0.001			<0.001
2000	132/236	1			1		
2001	241/433	0.99	0.72 to 1.36		1.05	0.74 to 1.49	
2002	188/431	0.61	0.44 to 0.84		0.58	0.41 to 0.82	
Outcome of first IVF ^b				0.011			0.01
0-1 oocyte	9/26	0.55	0.24 to 1.25		0.65	0.27 to 1.56	
≥2 oocytes	54/104	1.12	0.74 to 1.69		1.00	0.64 to 1.58	
Transfer	351/715	1			1		
Frozen	101/189	1.19	0.86 to 1.64		0.96	0.67 to 1.37	
Pregnancy	46/66	2.39	1.38 to 4.11		2.67	1.50 to 4.76	
Number of oocyte retrievals				0.072			0.01
1	158/299	1			1		
2	153/297	0.95	0.69 to 1.31		0.91	0.65 to 1.29	
3	125/224	1.13	0.80 to 1.60		1.06	0.73 to 1.54	
≥4	125/280	0.72	0.52 to 1.00		0.60	0.42 to 0.86	

^aAdjusted for all variables in the table and for IVF centre.

^bVariable corresponding to the step at which the first IVF failed, in five categories: less than two oocytes retrieved but no transfer; two or more oocytes retrieved but no transfer; embryos transferred but no embryo frozen and no pregnancy; embryos transferred and frozen but no pregnancy; pregnancy after fresh or frozen embryo transfer which resulted in an ectopic pregnancy, spontaneous abortion or stillbirth.

estimated to be 51% (95% CI 48 to 54). Another multiple imputation analysis was also conducted by considering only biological parenthood (Supplementary Table 1), leading to a biological parenthood achievement rate of 33% (95% CI 30 to 36). Sensitivity analysis gave similar results to the initial analysis, as the proportion of long-term parenthood achievement was estimated at 50% (95% CI 47 to 54) when considering biological and adoptive parenthood (versus 51% in the initial analysis) and at 33% (95% CI 29 to 38) when considering only biological parenthood (versus 33% in the initial analysis also).

Overall parenthood achievement during or after IVF treatment and paths to parenthood

Forty-one per cent (2691/6507) of couples become parents during IVF treatment in the centre and, among unsuccessfully treated couples, 51% became parents after having left the IVF centre; therefore, it was estimated that 71% ($0.41 + (1 - 0.41) \times 0.51$, 95% CI 69 to 74) of couples finally became parents during or after IVF treatment. The different paths to parenthood were explored on the basis of proportions observed in the postal survey. It included three main components (Figure 2): 48% of couples who became parents through medical treatment (in the IVF centre or afterwards), 12% after spontaneous conception and 11% through adoption.

Among the 539 couples remaining childless at the time of the survey, 27% (143/534) had undertaken steps to adopt a child without success, 5% (29/534) were still considering

adoption as a further step that could be undertaken, 41% (219/534) had considered adoption but finally decided against it and 27% (143/534) declared that adoption was never an option for them. The success rate of adoption was 60% (211/354) when considering couples who had become parents through adoption (211) and those who had unsuccessfully tried to adopt (143).

Discussion

In a large cohort of French couples treated by IVF and retrospectively followed up for 8 years, 71% finally succeeded in becoming parents, biologically and by adopting. Few studies have considered globally all the paths to parenthood among IVF couples, and most series have been relatively small (de La Rochebrochard et al., 2009; Lande et al., 2011; Sydsjö et al., 2011; Wischmann et al., 2012). Our results are similar to those of a German study conducted among 208 couples who began IVF in between 1994 and 1997, in which 66% of couples had become parents 10 years after starting IVF (Wischmann et al., 2012). Another study conducted among 1131 French couples had reported an overall cumulative parenthood rate of 60% 4-9 years after consulting for infertility (Walschaerts et al., 2012). Considering the shorter mean length of follow-up, and that the study population was restricted to couples with male infertility, this last result seems roughly in agreement with our estimation of 71%. Nonetheless, one Israeli study conducted among 134 couples who started IVF in between 2001

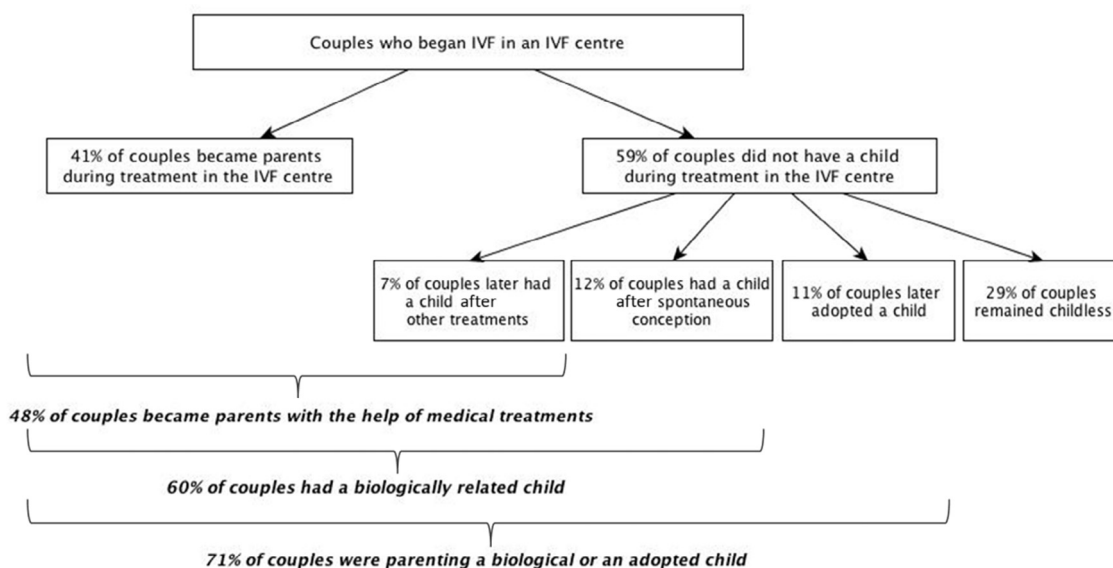


Figure 2 Long-term parenthood outcome of couples treated by IVF.

and 2002 has reported that 93% of couples had become parents 5–7 years after starting IVF (Lande et al., 2011). This higher parenthood achievement rate may probably be explained by the younger age of women included in the Israeli study (<35 years). A Norwegian study has also reported a higher rate of couples who became parents (83%) 10 years after starting IVF, but it was conducted among only 66 couples (Sundby et al., 2007). The heterogeneity of study populations and of lengths of follow-up probably explained variations in the previously reported proportions of couples who became parents. To the best of our knowledge, this paper is the first to estimate the overall cumulative parenthood achievement rate during and after IVF treatment in a large sample taking into consideration all couples treated by IVF whatever their age and origin of infertility. Moreover, the sensitivity analysis gave some reassuring evidence on the stability of the results obtained through multiple imputation strategy.

The chance of achieving parenthood decreases among older women, and further research will be needed to explore variations in parenthood achievement according to age. In our study population, 39% of women were aged 35 years or older at the beginning of IVF treatment, which is consistent with the proportion (41%) observed in the French national data for the year 2000 (Nyboe Andersen et al., 2004). The age of women treated by IVF tends to increase, with 46% of women aged 35 years or older in the French national data for the year 2011 (Kupka et al., 2016). This increasing age observed among treated couples reflects the general demographic trend to delay child-bearing described in European countries (Billari et al., 2006; Te Velde et al., 2012).

Although most couples became parents, IVF is far from being the only path to parenthood. In our study, the proportion of couples who became parents after treatment in the IVF centre (the CLBR) was 41%, an estimation very close to the 38% observed in a Japanese study (Bodri et al., 2014). In the long term, however, 71% of couples finally achieved their parenthood project biologically or by adoption. Of the couples unsuccessfully treated in the IVF centre, 51% became parents

after discontinuation of IVF treatment in this centre. This result is close to the rate reported in another small French study, where 46% of unsuccessfully treated couples became parents (de La Rochebrochard et al., 2009).

The probability of achieving parenthood biologically or by adoption after unsuccessful treatment was higher if the woman was younger, if during IVF treatment she had an ectopic pregnancy, a spontaneous abortion or a stillbirth, and if she had less than four IVF attempts in the IVF centre participating in the study. These factors could be mainly related to biological parenthood, as similar results were achieved when restricting the analysis to biological parenthood (Supplementary Table 1). Few results have been published on factors affecting parenthood achievement after unsuccessful treatment. In another French study, male and female ages less than 35 years and duration of infertility less than 24 months were associated with a higher cumulative biological parenthood rate, but it was conducted only in couples with male infertility (Walschaerts et al., 2012). Duration of infertility and female age have been reported to be associated with spontaneous pregnancy after failed assisted reproduction techniques in some studies (Khalili et al., 2012; Osmanagaoglu et al., 1999, 2002).

In our study, when considering the whole cohort, about 12% of couples became parents after spontaneous conception. This spontaneous live-birth rate seems to be intermediate compared with other published rates. In studies that have considered the different paths to parenthood, some have reported a lower spontaneous live birth rate of about 7% (Lande et al., 2011; Pinborg et al., 2009) and others a higher rate of about 15% (Sundby et al., 2007; Walschaerts et al., 2012). Although caution is required owing to heterogeneity of the populations, length of follow-up and outcome measures, other previously published studies have suggested that spontaneous live birth might finally concern one to two couples out of 10 (Brandes et al., 2010, 2011; Cahill et al., 2005; Ludwig et al., 2008; Osmanagaoglu et al., 2002; Shimizu et al., 1999). It is possible that some of these spontaneous live births were obtained with a new male partner (Kjaer et al., 2014). In our

postal study, however, only a low proportion (7%, 16/219) of spontaneous live births had been conceived with a new male partner.

Finally, in our study, about 11% of couples became parents through adoption. This estimation is in agreement with previous studies in which the proportion of IVF-treated couples who adopted ranged from 4–15% (Lande et al., 2011; Pinborg et al., 2007, 2009; Sundby et al., 2007; Walschaerts et al., 2012, 2013; Wischmann et al., 2012). Only one study has reported a higher proportion (21%), but this was a cumulative rate over a long follow-up period of 20 years (Sydsjö et al., 2011). Differences in adoption regulations from one country to another could partly explain disparities between published rates. However, adoption is much more an international process than a national one. For example, in France, 90% of children adopted are born abroad (Halifax and Villeneuve-Gokalp, 2005).

In conclusion, this study provides a complete longitudinal overview of paths to parenthood among couples successfully and unsuccessfully treated by IVF. These results should give hope to infertile couples, as seven out of 10 couples finally became parents 8 years after starting IVF treatment. However, IVF is not the only path to parenthood and couples should be informed of the other possible avenues.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2016.08.010.

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