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ARTICLE

# Medical factors associated with early IVF discontinuation<sup>☆</sup>

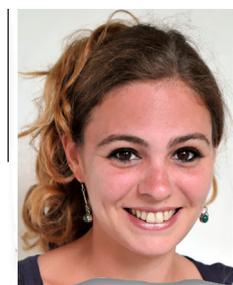


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Pénélope Troude is a public health MD and a PhD student in epidemiology, working on the long-term outcomes of couples treated by IVF.

**Abstract** Even when IVF is reimbursed by the social insurance system, as in France, high discontinuation rates have been reported and some patients drop out as soon as the first failed IVF cycle. This study aims to investigate medical factors associated with treatment discontinuation in an IVF centre after the first unsuccessful cycle. The study included 5135 couples recruited in eight French IVF centres and who had had an unsuccessful first IVF cycle in these centres in 2000–2002 (i.e. no live birth). Of these couples with a first failed IVF, 1337 did not have a second IVF in the centre (26%, 'early discontinuation group') and 3798 continued treatment with a second IVF in the centre. The characteristics of couples who discontinued IVF treatment were compared with those who continued using logistic regressions. Older women, women with duration of infertility >5 years, with female factor or unexplained infertility, with 0 or 1

oocyte retrieved and no embryo transfer during the first IVF were more likely to discontinue treatment early. Risk of early discontinuation was associated with medical factors that are also well known to be associated with impaired chance of successful IVF.   
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**KEYWORDS:** cohort study, dropout, infertility, IVF, medical factors, treatment discontinuation

## Introduction

Discontinuation of IVF is relatively common, since 25–50% of couples discontinue treatment as early as the first or second failed IVF cycle (Land et al., 1997; Malizia et al., 2009; Olivius et al., 2004b; Olivius et al., 2002; Sharma et al., 2002). These discontinuation rates may vary widely from one country to another depending on the country's policy on infertility treatment reimbursement (Dawson et al., 2005). Some countries make IVF access easier by covering from two to four IVF attempts, as for instance New Zealand, the Netherlands, Germany, France and Sweden (McDowell and Murray, 2011; Olivius et al., 2002; Smeenk et al., 2004). On the contrary, in the UK and in the USA, most patients have to finance their treatment themselves (Dawson et al., 2005; Sharma et al., 2002). In the UK, 64% of couples discontinued treatment after one unsuccessful IVF cycle (Sharma et al., 2002) and financial constraints are a major reason for this high early discontinuation rate (Goldfarb et al., 1997; McDowell and Murray, 2011). It may be assumed that dropout rates would be lower in countries where public funds cover IVF.

However, even in countries where IVF treatment is reimbursed, discontinuation rates remain relatively high. In the Netherlands, 32% of couples drop out before they have completed three IVF cycles and without achieving a live birth (Verhagen et al., 2008). In Germany, 39% of nonpregnant women dropped out after the first IVF cycle, whereas the first four cycles are covered (Schroder et al., 2004). In France, more than one-third of unsuccessfully treated couples discontinued IVF after the first failed cycle although the French welfare system fully reimburses up to four IVF cycles to obtain one pregnancy for heterosexual couples when the woman is aged <43 years (de La Rochebrochard et al., 2008). Treatment discontinuation is thus not only a financial matter and may be motivated by the heavy psychological or physical burden of IVF treatment and/or by a poor prognosis (Olivius et al., 2004b; Rajkhowa et al., 2006). The high discontinuation rate observed just after the first IVF cycle leads one to wonder who these couples are, who have begun IVF treatment but have dropped out very early even though they had no financial constraints.

Few studies have specifically investigated factors associated with IVF discontinuation (Brandes et al., 2009; Malizia et al., 2009; Pearson et al., 2009; Sharma et al., 2002; Soullier et al., 2011; Verberg et al., 2008). Factors associated with early discontinuation (after the first IVF attempt) have been even more rarely studied (Malizia et al., 2009; Pearson et al., 2009; Sharma et al., 2002). Only two studies have conducted multivariate analysis (Pearson et al., 2009; Verberg et al., 2008) and on small samples of <400 couples who discontinued IVF. A recent systematic review on discontinuation of infertility treatment underlined differences in the methodology used to

investigate predictors and lack of power in most of the studies, especially to detect small effect size (Gameiro et al., 2012). However, as reiterated in a recent meta-analysis of assisted reproduction compliance rates, success rates cannot be accurately estimated without considering discontinuation (Gameiro et al., 2013; Land et al., 1997; Soullier et al., 2008).

This study aims to investigate medical factors associated with early discontinuation of treatment in an IVF centre, in a large sample of couples who did not achieve a live birth after the first IVF cycle.

## Materials and methods

### Study population

The French DAIFI (Devenir Après Initiation d'un programme de FIV) cohort retrospectively included all 6507 couples who began IVF treatment (i.e. who had a first oocyte retrieval) between 2000 and 2002 in one of the eight participating IVF centres. The study received approval from the French Data Protection Authority in September 2005 (authorization number 05-1334).

Of these 6507 couples, 1372 had a live birth following the first IVF cycle (either following the fresh embryo transfer or following further transfers of frozen embryos) and 5135 did not achieve a live birth. The present study included these 5135 couples who did not achieve a live birth after the first IVF cycle in the centre. They were divided into two groups: those who discontinued treatment in the centre after the first failed IVF including fresh and frozen embryo transfers ( $n = 1337$ ) and those who continued treatment in the centre with a second IVF ( $n = 3798$ ). The couples of the discontinuation group did not have a second IVF in the centre during the follow-up period (i.e. until 2007). This corresponds to a minimum follow up of 5 years after the first IVF in the centre. However, some of these couples may have pursued IVF treatment in another IVF centre in France or abroad. All treatment interruptions in the IVF centre were included, whatever the reason for the interruption. Thus, some treatment interruptions could have been recommended by the clinician to the couple and the notion of treatment interruption does not correspond to that of noncompliance rates (Gameiro et al., 2013).

### Data collection

Medical data on all couples included in the cohort were obtained from electronic records of the IVF centres and covered the period 2000–2007. These data included fertility assessments (the woman's and man's ages and cause and duration of infertility), the number of IVF cycles in the centre, information on these cycles (number of oocytes retrieved, number of embryos obtained, number of embryos

**Table 1** Characteristics of couples according to continuation or discontinuation of treatment after the first failed IVF attempt.

	Continuing couples (n = 3798)	Discontinuing couples (n = 1337)	P-value*	Discontinuation rate
Woman's age (years)			<0.001	
<30	883 (23.2)	282 (21.2)		24.2
30–34	1415 (37.3)	400 (30.0)		22.0
35–39	1077 (28.4)	423 (31.7)		28.2
≥40	423 (11.1)	228 (17.1)		35.0
Man's age (years)			0.001	
<30	523 (13.8)	139 (10.6)		21.0
30–34	1296 (34.3)	421 (32.1)		24.5
35–39	1062 (28.1)	382 (29.2)		26.5
≥40	900 (23.8)	368 (28.1)		29.0
Duration of infertility (years)			<0.001	
0–2	761 (20.0)	221 (16.5)		22.5
3–4	1422 (37.4)	418 (31.3)		22.7
5–6	604 (15.9)	227 (17.0)		27.3
>6	516 (13.6)	270 (20.2)		34.4
Missing	495 (13.0)	201 (15.0)		28.9
Cause of infertility			<0.001	
Female factor	1357 (35.8)	519 (39.6)		27.7
Male factor	1272 (33.5)	363 (27.7)		22.2
Mixed	703 (18.5)	222 (16.9)		24.0
Unexplained	460 (12.1)	206 (15.7)		30.9

Values are *n* (%) or %. *P*-values for chi-squared test comparing couples' characteristics according to discontinuation or continuation of treatment after the first failed IVF cycle in the centre.

Calculation of discontinuation rate: e.g. among women aged <30 years, the discontinuation rate is 282/(282 + 883) = 282/1165 = 24.2%.

transferred, number of embryos frozen, number of frozen embryo transfers and pregnancy) and on the outcome of any ensuing pregnancies.

Reasons for discontinuation were not recorded in the medical files. However, this information was available for 299 couples (out of the 1337 couples who discontinued after the first failed IVF) who participated in a follow-up postal study in 2008–2010 carried out in all eight IVF centres (Trode et al., 2012).

### Characteristics and statistical analysis

The following characteristics were compared between couples who discontinued IVF treatment and those who pursued treatment after the first failed IVF (using the chi-squared test): the woman's age, the man's age and cause and duration of infertility (female, male, mixed or unexplained). Couples were also compared by characteristics of the first IVF cycle: number of oocytes retrieved, number of embryos transferred, total number of embryos frozen after the fresh transfer and number of frozen embryo transfers and the outcome of the transfer (no pregnancy, ectopic pregnancy, miscarriage, stillbirth). As these variables are strongly associated, they cannot be used together in a multivariate

model. Characteristics of the first failed IVF cycle were combined in one single variable named 'outcome of first failed IVF' corresponding to the step at which the IVF failed and consisting of five categories (<2 oocytes retrieved but no transfer; ≥2 oocytes retrieved but no transfer; fresh embryos transferred but no embryo frozen and no pregnancy; fresh embryos transferred and embryos frozen but no pregnancy; pregnancy after fresh or frozen embryo transfer which resulted in an ectopic pregnancy, miscarriage or stillbirth).

Univariate and multivariate logistic regressions were conducted to assess factors associated with discontinuation. All factors associated with discontinuation in the univariate analysis with a *P*-value <0.20 were included in the multivariate model. The model was adjusted for inclusion centre.

Statistical analyses were performed using STATA/SE 10.0 (Stata Press, College Station, TX, USA).

### Results

Among the 5135 couples included in the analysis, the median age of the women was 33 years (interquartile range, IQR, 30–37 years) and the median age of the men was

**Table 2** Characteristics and outcomes of the first failed IVF attempt according to continuation or discontinuation of treatment after the first failed IVF attempt.

	<i>Continuing couples (n = 3798)</i>	<i>Discontinuing couples (n = 1337)</i>	<i>P-value*</i>	<i>Discontinuation rate</i>
<b>Characteristics</b>				
Oocytes retrieved			<0.001	
0–1	90 (2.5)	92 (7.1)		50.5
2–3	360 (9.9)	145 (11.2)		28.7
4–9	1562 (42.9)	503 (38.9)		24.4
10–13	813 (22.4)	256 (19.8)		24.0
≥14	812 (22.3)	298 (23.0)		26.9
Fresh embryos transferred			<0.001	
0	389 (11.1)	177 (14.4)		31.3
1	429 (12.2)	171 (13.9)		28.5
2–3	2628 (74.9)	849 (68.9)		24.4
>3	64 (1.8)	36 (2.9)		36.0
Embryos frozen			<0.001	
0	2761 (79.0)	880 (71.3)		24.2
1–5	567 (16.2)	265 (21.5)		31.9
6–10	135 (3.9)	68 (5.5)		33.5
>10	33 (0.9)	21 (1.7)		38.9
Frozen embryo transfers			0.04	
0	3072 (80.9)	1066 (79.7)		25.8
1–3	719 (18.9)	263 (19.7)		26.8
>3	7 (0.2)	8 (0.6)		53.3
<b>Outcomes<sup>a</sup></b>				
0–1 Oocyte	40 (1.1)	47 (3.5)	<0.001	54.0
≥2 Oocytes	349 (9.2)	130 (9.7)		27.1
Fresh transfer	2554 (67.2)	847 (63.4)		24.9
Frozen	616 (16.2)	234 (17.5)		27.5
Pregnancy	239 (6.3)	79 (5.9)		24.8

Values are *n* (%). *P*-values for chi-squared test comparing the characteristics of the first failed IVF according to subsequent discontinuation or continuation of treatment in the centre.

Calculation of discontinuation rate: e.g. when 0 or 1 oocyte was retrieved during the first unsuccessful IVF, the discontinuation rate is  $92/(90 + 92) = 92/182 = 50.5\%$ .

<sup>a</sup>Variation corresponding to the step at which the first IVF attempt failed: 0–1 oocytes = <2 oocytes retrieved but no transfer; ≥2 oocytes = ≥2 oocytes retrieved but no transfer; fresh transfer = fresh embryos transferred but no embryo frozen and no pregnancy; frozen = fresh embryos transferred and embryos frozen but no pregnancy; pregnancy = pregnancy after fresh or frozen embryo transfer which resulted in an ectopic pregnancy, miscarriage or stillbirth.

35 years (IQR 31–39 years). The median duration of infertility was 3 years (IQR 4–5 years). For 32% of couples, infertility was due to a male factor, for 37% it was due to a female factor, and it was mixed for 18% of couples. Infertility was unexplained for 13% of couples. Couples had a median of two oocyte retrievals in the inclusion centre (IQR 1–3). Following the first oocyte retrieval, 89% of couples had a fresh embryo transfer.

Of these 5135 couples who did not have a live birth after the first IVF cycle including fresh and frozen embryo transfers, 26% discontinued treatment (i.e. did not have a second IVF cycle in the centre). In the discontinuation group, the

median year of the last transfer of fresh or frozen embryos was 2001 (IQR 2000–2002).

The characteristics of couples who continued and those who discontinued IVF treatment are compared in Table 1. Twenty-two percent of women aged 30–34 years discontinued, whereas 35% of women ≥40 years discontinued. Regarding cause of infertility, couples with unexplained infertility and couples with female factor infertility were more likely to discontinue treatment than couples with male or mixed factor infertility.

The characteristics of the first failed IVF attempt are presented in Table 2. All characteristics studied were

**Table 3** Univariate and multivariate analyses of characteristics and outcomes of first failed IVF cycle in couples associated with early IVF discontinuation.

Characteristics	No. of discontinuations/total no. of couples	Univariate analysis		Multivariate analysis (n = 5098)	
		OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Characteristics</b>					
Woman's age (years)			<0.01		<0.01
<30	282/1165	1.13 (0.95–1.34)		1.25 (1.04–1.49)	
30–34	400/1815	1		1	
35–39	423/1500	1.39 (1.19–1.63)		1.34 (1.14–1.58)	
≥40	228/651	1.91 (1.57–2.32)		1.91 (1.55–2.34)	
Duration of infertility (years)			<0.01		<0.01
0–2	221/982	0.99 (0.82–1.19)		1.00 (0.83–1.21)	
3–4	418/1840	1		1	
5–6	227/831	1.28 (1.06–1.54)		1.20 (0.99–1.46)	
>6	270/786	1.78 (1.48–2.14)		1.65 (1.36–2.00)	
Missing	201/696	1.38 (1.13–1.68)		1.89 (1.37–2.60)	
Cause of infertility			<0.01		<0.01
Male factor	519/1876	1		1	
Female factor	363/1635	1.34 (1.15–1.56)		1.33 (1.13–1.56)	
Mixed	222/925	1.11 (0.91–1.34)		1.15 (0.95–1.41)	
Unexplained	206/666	1.57 (1.28–1.92)		1.54 (1.25–1.91)	
<b>Outcomes<sup>a</sup></b>			<0.01		<0.01
0–1 oocyte	47/87	3.54 (2.31–5.44)		2.85 (1.82–4.48)	
≥2 oocytes	130/479	1.12 (0.91–1.39)		0.94 (0.74–1.18)	
Fresh transfer	847/3401	1		1	
Frozen	234/850	1.15 (0.97–1.36)		1.19 (0.99–1.43)	
Pregnancy	79/318	1.00 (0.76–1.30)		1.06 (0.81–1.39)	

Odds ratios are adjusted for all variables in the table and for inclusion centre.

<sup>a</sup>Variable corresponding to the step at which the first IVF attempt failed: 0–1 oocytes = <2 oocytes retrieved but no transfer; ≥2 oocytes = ≥2 oocytes retrieved but no transfer; fresh transfer = fresh embryos transferred but no embryo frozen and no pregnancy; frozen = fresh embryos transferred and embryos frozen but no pregnancy; pregnancy = pregnancy after fresh or frozen embryo transfer which resulted in an ectopic pregnancy, miscarriage or stillbirth.

significantly associated with treatment discontinuation. Considering outcome of the first failed IVF, when <2 oocytes were retrieved at the first IVF, half of the couples discontinued treatment. Discontinuation was higher when no embryo was transferred (31%), and even higher when >3 embryos were transferred (36%) compared with 2–3 embryos transferred (24%). Discontinuation increased from 24% when no embryo was frozen to 39% when >10 embryos were frozen. When <2 oocytes were retrieved and no embryo was transferred, 54% of couples discontinued treatment. When at least one embryo was transferred but not followed by a pregnancy and with no frozen embryo, only one-quarter of couples discontinued treatment.

Univariate and multivariate analyses are presented in Table 3. Adjustment only marginally modified the estimations of the odds ratios (OR). The J-shaped relationship between the woman's age and probability of discontinuation, with a minimum probability of discontinuation for women aged 30–34 years, remained after adjustment.

When duration of infertility was >6 years, probability of discontinuation tended to increase with the duration. Couples with female infertility and couples with unexplained infertility were more likely to discontinue treatment than couples with male infertility. The outcome of the first failed IVF attempt remained significantly associated with probability of discontinuation after adjustment ( $P < 0.01$ ). In particular, the adjusted OR for retrieval of 0 or 1 oocyte and no embryo transfer was 2.85 (95% CI 1.82–4.48) compared with couples who had an embryo transfer.

Reasons for discontinuation are presented in Table 4, using categories defined by Gameiro et al. (2012). The descriptors used in the postal questionnaire are presented in Supplementary Table 1 (available online). The main reasons for discontinuation were patient related, in particular the perception of a poor prognosis reported by 13% of couples. The psychological and physical burden of treatment was reported by 15% of couples. Only 6% (95% CI 3.3–8.7%) declared that change of IVF centre was the reason for

**Table 4** Main reasons for discontinuation given in a follow-up survey among the couples who discontinued treatment after the first failed IVF attempt.

Category	Subcategory	Response (n = 299)	
Treatment (15.4%)	Psychological burden of treatment	32 (10.7)	
	Physical burden of treatment	14 (4.7)	
Clinic (9.7%)	Clinic--related issues	29 (9.7)	
	Patient related (38.8%)	Relational problems	9 (3.0)
Patient related (38.8%)	Perception of poor prognosis	39 (13.0)	
	Logistic/practical reasons	2 (0.7)	
	Personal reasons	6 (2.0)	
	Adoption	22 (7.4)	
	Other parenting options	16 (5.4)	
	Abandonment of childwish	7 (2.3)	
	Postponement of treatment	15 (5.0)	
	External constraints (4.3%)	Doctor censoring	4 (1.3)
		Financial issues	4 (1.3)
		Health problems	5 (1.7)
Noninterpretable (28.8%)	Went to other clinics	18 (6.0)	
	Other/unknown/not reported	68 (22.8)	
Supplementary category (3.0%)	Spontaneous live birth	9 (3.0)	

Values are *n* (%). Categories are those used by [Gameiro et al. \(2012\)](#) except for the supplementary category, which has been added in this study.

discontinuation. However, a high proportion of couples (23%) did not give any reason.

## Discussion

After a first failed IVF cycle including fresh and frozen embryo transfers, more than one couple out of four (26%) discontinued IVF treatment in the eight French centres participating in this study. This is a very high rate of early discontinuation, especially considering the fact that four IVF cycles are reimbursed in France for heterosexual couples with a woman aged <43 years. However, this result is in agreement with a recent meta-analysis of assisted reproduction compliance rates in which the only French study (on a very large sample, *n* = 8362) exhibited a much lower compliance rate than studies in other countries ([Gameiro et al., 2013](#); [Rufat et al., 1994](#)). As in most studies, the current study cannot rule out the possibility that some couples pursued IVF in another centre ([Gameiro et al., 2013](#)). However, results on reason for discontinuation suggested that this was the case for a very limited number of couples (6%). Moreover, medical factors associated with IVF discontinuation were studied among couples who had discontinued treatment mostly between 2000 and 2002. It is thus possible that behaviour regarding IVF discontinuation has changed during recent years.

This study principally investigated factors associated with these early discontinuations and found that, globally, couples with poor prognostic factors had a higher risk of early discontinuation of IVF treatment. In particular, early discontinuation was associated with women >34 years, with duration of infertility >6 years, with 0 or 1 oocyte retrieved and no embryo transfer at the first IVF cycle. Early discontinuation was also associated with the cause

of infertility, with higher risk for female or unexplained infertility. All these factors remained significantly associated with the probability of discontinuation in the multivariate analysis. Moreover, study of medical factors associated with early discontinuation in the subgroup of couples who had participated in the postal study (*n* = 1711 including 299 who had discontinued treatment after the first failed IVF) yielded results (Supplementary Table 2) very close to those observed in the total study population (*n* = 5135).

Regarding the woman's age, the results are in line with most previous studies that reported a higher probability of discontinuation among older women ([Brandes et al., 2009](#); [Malizia et al., 2009](#); [McDowell and Murray, 2011](#); [Pearson et al., 2009](#); [Sharma et al., 2002](#); [Soullier et al., 2011](#)). Nevertheless, for the first time as far as is known, the current study exhibited a J-shaped relationship between the woman's age and probability of early IVF discontinuation in both univariate and multivariate analyses. Such a J-shaped relationship has already been exhibited for the effect of the woman's age on various reproductive outcomes, such as IVF success rates, which follow an inverse J-shape ([Soullier et al., 2011](#); [Templeton et al., 1996](#)), or risk of spontaneous abortion, which follows a J-shape ([Nybo Andersen et al., 2000](#)). In the current study, infertility of >6 years duration was significantly associated with a higher proportion of early discontinuation (34% versus 22–23% if duration of infertility ≤4 years). Very few studies have investigated the association between duration of infertility and discontinuation ([Brandes et al., 2009](#); [Verberg et al., 2008](#)). The current results are in agreement with a study carried out in the Netherlands that reported 26% of discontinuation at all stages of fertility care when duration of infertility was 2–5 years versus 86% when duration of infertility was >5 years ([Brandes et al., 2009](#)). However, the

latter study differed from ours in two main points: data on treatment cycles followed in another hospital were taken into account and the minimum length of follow up was 2 years. Investigating factors associated with discontinuation before the third IVF cycle, Verberg et al. (2008) did not find a significant association with duration of infertility. However, they postulated a linear relationship between probability of discontinuation and duration of infertility, whereas the current results suggested a significant impact only after 6 years.

More couples with unexplained infertility discontinued IVF treatment early (31%) than couples with male factor infertility (22%). The few studies that have explored discontinuation in relation to cause of infertility also suggested an association between cause and discontinuation, but they reached contradictory conclusions on the direction of this association (Brandes et al., 2009; Pouly et al., 2012; Verberg et al., 2008). Unexplained infertility was associated with a lower proportion of discontinuation of fertility care in a study conducted in the Netherlands (Brandes et al., 2009). In the current study, the higher proportion of early discontinuation observed among couples with unexplained infertility could be linked to a higher chance of spontaneous pregnancy in this subpopulation (Troude et al., 2012). In fact, among 437 couples with unexplained infertility, Brandes et al. (2011) reported that almost three-quarters of ongoing pregnancies were spontaneous. Male infertility was associated with a greater proportion of discontinuation in two studies carried out in the Netherlands, one investigating discontinuation before the third IVF cycle and the other discontinuation at all stages of fertility care (Brandes et al., 2009; Verberg et al., 2008). Contradictory results could be due to a differential effect of this variable according to the type of discontinuation: early discontinuation, discontinuation at any stage of IVF treatment or discontinuation at any stage of fertility care. Further study would be required to confirm and to analyse in detail such a differential effect. It could also reflect differences between countries or centres within a country in the medical counselling given to couples according to the cause of infertility.

Regarding outcome of the first failed IVF cycle, the proportion of early discontinuation was very high (54%) when the IVF attempt failed as early as its first step (0 or 1 oocyte retrieved and no embryo transfer). When the first step went well, there were no clear differences in early discontinuation whatever the course after this first step of the failed IVF attempt (fresh embryo transfer, frozen embryo transfers, pregnancy). The higher proportion of discontinuation among women with no or few oocytes retrieved is in agreement with two previous studies carried out in Britain and in France (Pouly et al., 2012; Sharma et al., 2002) and in contradiction with one US study (Pearson et al., 2009). In the British study (Sharma et al., 2002), retrieval of  $\leq 5$  oocytes was associated with a higher proportion of discontinuation (77% versus 60%,  $P < 0.05$ ) whereas in the US study (Pearson et al., 2009), biochemical pregnancy and spontaneous abortion were associated with a greater probability of discontinuation. Unexpectedly, in the current study, the rate of discontinuation increased with the number of frozen embryos, whereas a high number of frozen embryos is a good

prognostic factor. In France, couples are not allowed to have a new IVF cycle as long as they have frozen embryos from a previous cycle. The higher proportion of discontinuation among couples with many frozen embryos could be explained by a higher level of burden in these couples related to numerous transfers; however, this concerns a very limited number of couples in this study.

The factors associated with a higher risk of early discontinuation were also those well known to be associated with impaired chances of successful IVF: older age of the woman, longer duration of infertility, low ovarian response to hormonal stimulation leading to retrieval of 0 or 1 oocyte during the first failed IVF attempt (Kupka et al., 2003; van Loendersloot et al., 2010). The current study does not elucidate whether discontinuation was suggested by the medical staff or if it was purely the couple's decision. Both hypotheses are possible, as it has been suggested that the couple's perception of their prognosis may influence their choice to continue the treatment or not (Gameiro et al., 2013; Sharma et al., 2002). This has been referred to as 'self-diagnosed poor prognosis' (Penzias, 2004). A poor perceived prognosis could also be associated with stress (Rajkhowa et al., 2006; Verberg et al., 2008). Psychological burden of treatment or emotional distress are well-known risk factors for IVF treatment discontinuation (Domar et al., 2010; Goldfarb et al., 1997; McDowell and Murray, 2011; Olivius et al., 2004a; Rajkhowa et al., 2006; Smeenk et al., 2004; Van den Broeck et al., 2009). In the current study, perception of poor prognosis or psychological burden of treatment was reported by almost one-quarter of couples who had discontinued treatment after the first failed IVF and who participated in the postal follow-up study. It is thus possible that self-diagnosed poor prognosis leads to an increase in patients' stress and that both factors, self-diagnosed poor prognosis and increasing stress, lead to a higher risk of early IVF discontinuation. However, self-diagnosed poor prognosis is a very different notion from 'medically diagnosed poor prognosis'. In a Canadian study, a substantial proportion of couples who cited poor prognosis as a reason for discontinuation actually had a favourable prognosis (Malcolm and Cumming, 2004). This result may reflect patients losing hope of success before medical staff or different definitions of poor prognosis (Boivin et al., 2012). Moreover, other factors such as social relations (especially family support) may also have an impact on the decision to discontinue treatment (Vassard et al., 2012). Finally, it should be noted that investigating reasons of discontinuation raised issues such as how to define discontinuation and when to assess it. Indeed, as underlined by Gameiro et al. (2012), the retrospective design used in most studies makes it difficult to distinguish cause from effect and to determine whether the reason reported was the reason at time of discontinuation or has emerged later. The high proportion of couples who did not specify their reason for discontinuation (68/299, or 23%) among those who completed and returned the postal questionnaire probably reflects this difficulty and leads to the results on reasons of discontinuation being interpreted with caution.

To conclude, investigating objective medical factors associated with early IVF discontinuation (whatever the reason for discontinuation), patients with poor prognostic factors are more likely to discontinue treatment after a first

failed IVF. A next step would be to examine whether the early discontinuation results from a decision of the couple themselves (and how it is linked to their level of stress and to the psychological burden of the treatment), from medical staff counselling or from a combination of the two. Further studies are needed to understand how these prognostic factors weigh on the decision of the couple and/or the medical staff to discontinue IVF.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.rbmo.2013.10.018>.

## References

- Boivin, J., Domar, A.D., Shapiro, D.B., Wischmann, T.H., Fauser, B.C., Verhaak, C., 2012. Tackling burden in ART: an integrated approach for medical staff. *Hum. Reprod.* 27, 941–950.
- Brandes, M., van der Steen, J.O., Bokdam, S.B., Hamilton, C.J., de Bruin, J.P., Nelen, W.L., Kremer, J.A., 2009. When and why do subfertile couples discontinue their fertility care? A longitudinal cohort study in a secondary care subfertility population. *Hum. Reprod.* 24, 3127–3135.
- Brandes, M., Hamilton, C.J., van der Steen, J.O., de Bruin, J.P., Bots, R.S., Nelen, W.L., Kremer, J.A., 2011. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. *Hum. Reprod.* 26, 360–368.
- Dawson, A.A., Diedrich, K., Felberbaum, R.E., 2005. Why do couples refuse or discontinue ART? *Arch. Gynecol. Obstet.* 273, 3–11.
- de La Rochebrochard, E., Soullier, N., Peikrishvili, R., Guibert, J., Bouyer, J., 2008. High in vitro fertilization discontinuation rate in France. *Int. J. Gynaecol. Obstet.* 103, 74–75.
- Domar, A.D., Smith, K., Conboy, L., Iannone, M., Alper, M., 2010. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. *Fertil. Steril.* 94, 1457–1459.
- Gameiro, S., Boivin, J., Peronace, L., Verhaak, C.M., 2012. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. *Hum. Reprod. Update* 18, 652–669.
- Gameiro, S., Verhaak, C.M., Kremer, J.A., Boivin, J., 2013. Why we should talk about compliance with assisted reproductive technologies (ART): a systematic review and meta-analysis of ART compliance rates. *Hum. Reprod. Update* 19, 124–135.
- Goldfarb, J., Austin, C., Lisbona, H., Loret de Mola, R., Peskin, B., Stewart, S., 1997. Factors influencing patients' decision not to repeat IVF. *J. Assist. Reprod. Genet.* 14, 381–384.
- Kupka, M.S., Dorn, C., Richter, O., Felberbaum, R., van der Ven, H., 2003. Impact of reproductive history on in vitro fertilization and intracytoplasmic sperm injection outcome: evidence from the German IVF Registry. *Fertil. Steril.* 80, 508–516.
- Land, J.A., Courtar, D.A., Evers, J.L., 1997. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. *Fertil. Steril.* 68, 278–281.
- Malcolm, C.E., Cumming, D.C., 2004. Follow-up of infertile couples who dropped out of a specialist fertility clinic. *Fertil. Steril.* 81, 269–270.
- Malizia, B.A., Hacker, M.R., Penzias, A.S., 2009. Cumulative live-birth rates after in vitro fertilization. *N. Engl. J. Med.* 360, 236–243.
- McDowell, S., Murray, A., 2011. Barriers to continuing in vitro fertilisation – why do patients exit fertility treatment? *Aust. N. Z. J. Obstet. Gynaecol.* 51, 84–90.
- Nybo Andersen, A.M., Wohlfahrt, J., Christens, P., Olsen, J., Melbye, M., 2000. Maternal age and fetal loss: population based register linkage study. *Br. Med. J.* 320, 1708–1712.
- Olivius, C., Friden, B., Borg, G., Bergh, C., 2004a. Psychological aspects of discontinuation of in vitro fertilization treatment. *Fertil. Steril.* 81, 276.
- Olivius, C., Friden, B., Borg, G., Bergh, C., 2004b. Why do couples discontinue in vitro fertilization treatment? A cohort study. *Fertil. Steril.* 81, 258–261.
- Olivius, K., Friden, B., Lundin, K., Bergh, C., 2002. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. *Fertil. Steril.* 77, 505–510.
- Pearson, K.R., Hauser, R., Cramer, D.W., Missmer, S.A., 2009. Point of failure as a predictor of in vitro fertilization treatment discontinuation. *Fertil. Steril.* 91, 1483–1485.
- Penzias, A.S., 2004. When and why does the dream die? Or does it? *Fertil. Steril.* 81, 274–275.
- Pouly, J.L., Ouziel, L., Gremeau, A.S., De Mouzon, J., Janny, L., Vignancour, S., Dejoul, L., Brugnon, F., 2012. Analyse des facteurs influençant les taux cumulatifs d'accouchement en AMP sur une cohorte de 1001 couples. *Gynecol. Obstet. Fertil.* 40, 219–225.
- Rajkhowa, M., McConnell, A., Thomas, G.E., 2006. Reasons for discontinuation of IVF treatment: a questionnaire study. *Hum. Reprod.* 21, 358–363.
- Rufat, P., Roulier, R., Belaisch-Allart, J., Bachelot, A., de Mouzon, J., 1994. Evolutions des critères pronostiques de décondation in vitro selon le rang de la tentative. *FIVNAT. Contracept. Fertil. Sex.* 22, 282–286.
- Schroder, A.K., Katalinic, A., Diedrich, K., Ludwig, M., 2004. Cumulative pregnancy rates and drop-out rates in a German IVF programme: 4102 cycles in 2130 patients. *Reprod. Biomed. Online* 8, 600–606.
- Sharma, V., Allgar, V., Rajkhowa, M., 2002. Factors influencing the cumulative conception rate and discontinuation of in vitro fertilization treatment for infertility. *Fertil. Steril.* 78, 40–46.
- Smeenk, J.M., Verhaak, C.M., Stolwijk, A.M., Kremer, J.A., Braat, D.D., 2004. Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. *Fertil. Steril.* 81, 262–268.
- Soullier, N., Bouyer, J., Pouly, J.L., Guibert, J., de La Rochebrochard, E., 2008. Estimating the success of an in vitro fertilization programme using multiple imputation. *Hum. Reprod.* 23, 187–192.
- Soullier, N., Bouyer, J., Pouly, J.L., Guibert, J., de La Rochebrochard, E., 2011. Effect of the woman's age on discontinuation of IVF treatment. *Reprod. Biomed. Online* 22, 496–500.
- Templeton, A., Morris, J.K., Parslow, W., 1996. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 348, 1402–1406.
- Troude, P., Bailly, E., Guibert, J., Bouyer, J., de la Rochebrochard, E., 2012. Spontaneous pregnancies among couples previously treated by in vitro fertilization. *Fertil. Steril.* 98, 63–68.

- Van den Broeck, U., Holvoet, L., Enzlin, P., Bakelants, E., Demyttenaere, K., D'Hooghe, T., 2009. Reasons for dropout in infertility treatment. *Gynecol. Obstet. Invest.* 68, 58–64.
- van Loendersloot, L.L., van Wely, M., Limpens, J., Bossuyt, P.M., Repping, S., van der Veen, F., 2010. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. *Hum. Reprod. Update* 16, 577–589.
- Vassard, D., Lund, R., Pinborg, A., Boivin, J., Schmidt, L., 2012. The impact of social relations among men and women in fertility treatment on the decision to terminate treatment. *Hum. Reprod.* 27, 3502–3512.
- Verberg, M.F., Eijkemans, M.J., Heijnen, E.M., Broekmans, F.J., de Klerk, C., Fauser, B.C., Macklon, N.S., 2008. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum. Reprod.* 23, 2050–2055.
- Verhagen, T.E., Dumoulin, J.C., Evers, J.L., Land, J.A., 2008. What is the most accurate estimate of pregnancy rates in IVF dropouts? *Hum. Reprod.* 23, 1793–1799.

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