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Spontaneous pregnancies among couples previously treated by in vitro fertilization

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None of the authors have any conflict of interest.

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Capsule: Among couples previously treated by IVF, one in five has a live birth following a spontaneous pregnancy. This should give hope to unsuccessfully treated couples, especially young couples with unexplained infertility.

ABSTRACT

Objective: To determine the frequency of live births following spontaneous pregnancy (BSP) and to examine their associated factors among couples who have unsuccessfully or successfully experienced fertility treatments.

Design: Retrospective cohort.

Setting: Eight French IVF centers.

Patients: 2,134 couples who began IVF treatment in the centers in 2000-2002 and were followed up by a postal questionnaire sent 7-9 years after they started treatment in the inclusion center.

Interventions: None.

Main outcome measures: Rates of live birth following spontaneous pregnancy, factors associated with BSP. Univariate and multivariate analyses were conducted using logistic regression.

Results: The BSP rate was 17% (218/1,320) among couples who had previously had a child through medical treatment and 24% (193/814) among couples who had remained childless after treatment. In both groups, the probability of BSP was higher among younger women and increased with a smaller number of IVF attempts. Probability was also higher when the cause of infertility was unexplained.

Conclusions: Our results should give hope to couples who have been unsuccessfully treated by IVF, especially young couples with unexplained infertility. Nonetheless, it should be remembered that the BSP rates are cumulative rates observed over a long period of time and that these couples have a very low monthly probability of conceiving.

Keywords: Fertilization in vitro, spontaneous pregnancy, follow-up studies, France

INTRODUCTION

The issue of live births following spontaneous pregnancy (BSP) among infertile couples who have had in vitro fertilization (IVF) treatment may seem an unusual one in such a context (1) and may appear anecdotal to physicians, especially if treatment has failed (2). However, in view of some recent publications, BSP after IVF may not be such a rare occurrence.

The question of spontaneous pregnancies has been approached in studies on drop-out from fertility care, since 5% to 7% of couples may have dropped out from the IVF waiting list because of spontaneous pregnancy (3-5). Because these studies focused only on reasons for treatment dropout, BSP that occurred at a later date were not taken into account. Some studies have evaluated occurrence of BSP specifically among couples who previously had a child through IVF and intracytoplasmic sperm injection (ICSI) (1, 2, 6). Reported BSP rates ranged from 16% to 17% with a follow-up between two and five years. In another recent study conducted in Denmark, rate of delivery after spontaneous pregnancy among couples who had previously conceived through intrauterine insemination or assisted reproduction techniques was 17% five years after treatment initiation (7). Other studies have focused on couples who had been unsuccessfully treated by IVF or ICSI and the BSP rate varied considerably (8-11). With various durations of follow-up (two to ten years), most of these studies reported spontaneous pregnancy or BSP rates that ranged from 11% to 19%, except one that observed a BSP rate as high as 32% (9).

Comparison between studies on BSP is difficult since the populations (infertile couples or treated couples), outcome (pregnancy or live birth) and duration of follow-up differ considerably. Moreover, most studies of unsuccessfully treated couples included less than 200 couples. Although the results varied widely, all published studies showed that BSP may

occur after IVF in as many as one or two couples out of 10. Our objective was to estimate the spontaneous live birth rate and to examine its associated factors among couples who had received IVF treatment for infertility, whether successfully or unsuccessfully.

MATERIALS AND METHODS

The DAIFI cohort

The DAIFI cohort (Outcome after In Vitro Fertilization treatment Initiation) is a retrospective cohort including couples who had begun IVF treatment between 2000 and 2002 in one of the eight participating French IVF centers (the inclusion centers). This study received Institutional Review Board approval from the French Data Protection Authority (authorization number 05-1334). Information on long-term outcome was collected by postal questionnaire completed by the couples from 2008 through 2010. The questionnaire included sociodemographic information, fertility and medical treatment history, occurrence of spontaneous pregnancies and recourse to adoption. Of the 4,029 couples contacted, 2,321 completed the postal questionnaire. Analysis was restricted to 2,134 couples who were still together at the time of study (187 separated couples were excluded).

Two study groups: successfully and unsuccessfully treated couples

The 2,134 couples were divided into two groups: the “*successfully treated group*” of 1,320 couples who had had a child during medical treatment and the “*unsuccessfully treated group*” of 814 couples who remained childless after medical treatment. Success during medical treatments included all births following IVF treatment in the inclusion center as well as all births following other medical treatments (ovarian stimulation, surgery, artificial insemination with partner sperm or donor sperm, oocyte donation, IVF, ICSI, FET) subsequently received in France or abroad.

Births following spontaneous pregnancies

Births following spontaneous pregnancies (BSP) were declared by the couple in the postal questionnaire. The date of the birth was recorded. Based on the medical records, information on the dates of first and last IVF attempt in the inclusion center were collected. For successfully treated couples, the date of birth following medical treatment was collected.

Statistical analyses

The occurrence and distribution of BSP were studied separately in each group. The two groups were not compared as time of exposure to conception could vary between the two groups and could not be properly controlled based on the retrospective data collected in this study. In particular, periods of contraception may have differed between the two groups and the corresponding dates were not asked because of the retrospective design of the study over several years. Moreover, the exposure time was defined differently in each group: for successfully treated couples, it was defined as the time since birth following treatment; for unsuccessfully treated couples, it was defined as the time since the last attempt in the inclusion center (i.e. last fresh or frozen embryo transfer).

The couples' characteristics were analyzed in relation to BSP. Categorical variables were compared using the chi-2 test, and quantitative variables were described as median, first and third quartiles (Q1-Q3). Couples' characteristics included the woman's and the man's age at the first IVF attempt (< 30, 30-34, 35-39, ≥ 40 years) and the highest educational level of the couple (less than, equal to or higher than the French high school diploma). Medical characteristics were extracted from the inclusion IVF center database and included type of infertility (primary vs secondary), cause of infertility (female factor, male factor, mixed, unexplained), its duration (defined as the interval between first attempting pregnancy and first oocyte retrieval), characteristics at the first attempt in the inclusion center (number of

oocytes retrieved, number of oocytes fertilized, number of embryos transferred, number of embryos frozen), overall characteristics of treatment in the center (number of attempts, number of frozen embryo transfers (FET), at least one embryo transferred, at least one pregnancy obtained). Information on the path followed by the couples included treatments before and after IVF in the inclusion center and initiation of adoption procedures. Multivariate analyses were conducted to assess factors associated with BSP using logistic regression. Multivariate models were adjusted for inclusion center and included the following variables: the woman's age, duration of infertility, cause of infertility, having a child before IVF in the inclusion center and other variables associated with BSP with a *P* value <0.20. Some variables were excluded because of colinearity, such as the man's age. All statistical analyses were performed using STATA/SE 10.0 (Stata Press, College Station, TX, USA).

RESULTS

In the *successfully treated group* (n=1,320), the women's median age at the first IVF attempt in the inclusion center was 32 years (Q1-Q3[29-35]). Infertility was due to a female factor in 32%, a male factor in 37%, to both in 18% and was unexplained in 13%. Ninety-one percent of live births were obtained through IVF in the inclusion center, 6.5% through IVF in another center and 3% through other treatments (mainly artificial insemination). Among these successfully treated couples followed up for a median of 6 years, 218 later had a spontaneous live birth, a BSP rate of 17% (95% CI: 15%, 19%). BSP distribution over time is presented in figure 1. Most BSP occurred during the third or fourth year after the birth following medical treatment. The median time between the first birth following medical treatment and the birth following spontaneous conception was 33 months [22-42].

In the *unsuccessfully treated group* (n=814), the women's median age at the first attempt in the inclusion center was 34 years [31-38]. Infertility was due to a female factor in 43%, a male factor in 28%, to both in 17% and was unexplained in 12%. Eighteen percent of couples had undergone other unsuccessful treatments after IVF in the inclusion center. Among the 814 unsuccessfully treated couples followed up for a median of 7 years since the last IVF attempt in the inclusion center, 193 BSP were reported, or 24% (95% CI: 21%, 27%). The median time elapsed since the initial pregnancy attempt was 6 years [5-7]. BSP distribution over time since the last attempt in the inclusion center is presented in figure 2. Almost 60% of BSP occurred during the first two years after the last IVF attempt in the inclusion center.

Characteristics of couples were compared in relation to BSP in the *successfully treated group* and in the *unsuccessfully treated group* in Table 1. Five variables were significantly

associated with BSP in both groups in the univariate analysis: BSP was more frequent when the woman and the man were younger, when the infertility was unexplained, when the technique used at the first attempt was IVF without ICSI and when the number of IVF attempts undergone by the couple in the inclusion center was small. In the *successfully treated group*, BSP was also more frequent when the couple had already had treatment before attending the inclusion center and when the couple did not have FET in the inclusion center. In the *unsuccessfully treated group*, BSP was also more frequent when the duration of infertility was shorter and when two embryos were transferred at the first IVF attempt in the inclusion center. Multivariate analysis is presented in Table 2. In both groups, the probability of BSP decreased as the woman's age increased and the number of IVF attempts in the inclusion center was greater ($P < 0.001$ for trend). Probability increased when infertility was due to a female factor and above all when it was unexplained. Two variables were significant in the multivariate analysis only in the *unsuccessfully treated group*: for these couples, the probability of BSP also increased when the duration of infertility decreased and when at least one embryo was transferred during treatment in the inclusion center.

DISCUSSION

In a large sample of French couples undergoing IVF treatment for infertility, the rate of live birth following spontaneous pregnancy was estimated to be 17% (15 to 19%) among successfully treated couples and 24% (21 to 27%) among unsuccessfully treated couples. Among unsuccessfully treated couples, 60% of BSP occurred in the two years following the last IVF transfer, suggesting that BSP was the reason for IVF treatment discontinuation (usually the duration between two attempts was no more than 18 months). Among successfully treated couples, 58% of BSP occurred during the third and fourth years after the first birth following medical treatment. Thus, the context of BSP is clearly quite different in these two groups. Moreover, the BSP rate observed among successfully and unsuccessfully treated couples cannot be directly compared because couples who had had a child through fertility treatment had been exposed to the possibility of BSP during a shorter period of time (because of the pregnancy period). Furthermore, couples who obtained the desired child through fertility treatment may be less likely to try to conceive again and the study did not include enough information to properly control for such differences in time of exposure to conception between the two groups (for example contraceptive periods were unknown).

The BSP rate observed among *successfully treated couples*, 17%, was very close to the 16-17% observed in other studies in Germany, Denmark and Japan (2, 6, 7). In our study, the median time to BSP after the birth of a child following medical treatment was three years, which is in accordance with previous reports (1, 2). The BSP rate observed among *unsuccessfully treated couples*, 24%, appears to be slightly higher than most of those previously reported in the literature, usually lower than 17%-(8, 12, 13). However, one English study has already reported a much higher BSP rate of 32% four to ten years after

referral to a center, in couples who had ceased to try to conceive by assisted reproduction techniques (9). Previous studies concerned samples of less than 250 couples, whereas our study has been conducted on more than 800 *unsuccessfully treated couples*.

In prospective and retrospective cohort studies, information cannot be gathered for all couples: in our cohort, 58% of contacted couples participated in the postal survey seven to nine years after IVF initiation in the inclusion center. This participation rate is higher than that (44%) observed in an English cohort of couples who had undergone IVF four to ten years earlier (9). Most studies did not report their participation rates, which may have been even lower. We cannot rule out the possibility that couples who had a BSP are more likely to respond than couples who did not, and so published BSP rates may be slightly overestimated.

Regarding factors associated with BSP, for both successfully and unsuccessfully treated couples the probability of BSP decreased as the woman's age increased, as previously reported in the literature (1, 6, 9, 14, 15). The cause of infertility was globally associated with BSP among *successfully treated couples* and among *unsuccessfully treated couples*. The proportion of BSP was higher for couples with unexplained infertility and lower for male-factor infertility. Previously reported results on cause or type of infertility are mixed: cause or diagnosis of infertility have been reported as associated factors in some studies (1, 9, 14) and not in others (6, 15, 16). For *unsuccessfully treated couples*, we observed 32% of BSP among couples with unexplained infertility while Cahill et al. reported 35% of spontaneous pregnancy in this subpopulation within three years after IVF treatment (9). Other medical characteristics also seemed linked to BSP, especially among *unsuccessfully treated couples*. The proportion of BSP decreased when the number of IVF attempts increased in the *successfully* and in *the unsuccessfully treated groups*, but the impact of this variable seemed

much greater in the *unsuccessfully treated group*. Other variables were significant in the multivariate model only among the *unsuccessfully treated couples*: duration of infertility and at least one embryo transfer during the treatment in the inclusion center. Globally, factors associated with BSP can be viewed as indicators of a better fertility prognosis, especially among *unsuccessfully treated couples*: couples with BSP are younger and they have better medical characteristics (shorter duration of infertility and at least one embryo transfer during IVF treatment). Unexplained infertility appeared strongly associated with BSP (17), and could probably also be interpreted as an indicator of better fertility prognosis compared with couples whose infertility is of known origin, and particularly of male-factor origin. In the *unsuccessfully treated group*, the BSP rate in couples with unexplained infertility and a woman's age under 35 years was as high as 45% ($n = 21/47$; 95% CI: 30%, 60%). Considering the 37 couples with the best prognostic factors (unexplained infertility, woman's age under 35 years and infertility duration ≤ 5 years), this rate even reached 57% (95% CI: 39%, 73%). This result is in agreement with a study conducted in the Netherlands on the reasons for dropping out from a waiting list for IVF: spontaneous pregnancies occurred mostly in couples with unexplained infertility and younger than 35 years (5). Based on these results, it would be very interesting to develop further research with the specific aim of better characterizing young couples with unexplained infertility. However, these couples only represent a small proportion of all unsuccessfully treated couples, at least in our French population.

To conclude, our results should give hope to couples who have previously been treated by IVF, especially for unsuccessful young couples with unexplained infertility. Nonetheless, it should be borne in mind that the published rates are cumulative BSP observed over a long period of time. For example, if *unsuccessfully treated couples* had a cumulative BSP rate of

24%, they had to wait a median of six years to have their child. This corresponds to a very low monthly conception probability (fecundability) of around 0.44%, whereas fecundability in the general population is estimated at 25% (18).

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Figure 1. Distribution of BSP over time since birth following treatments among successfully treated couples (n = 218)

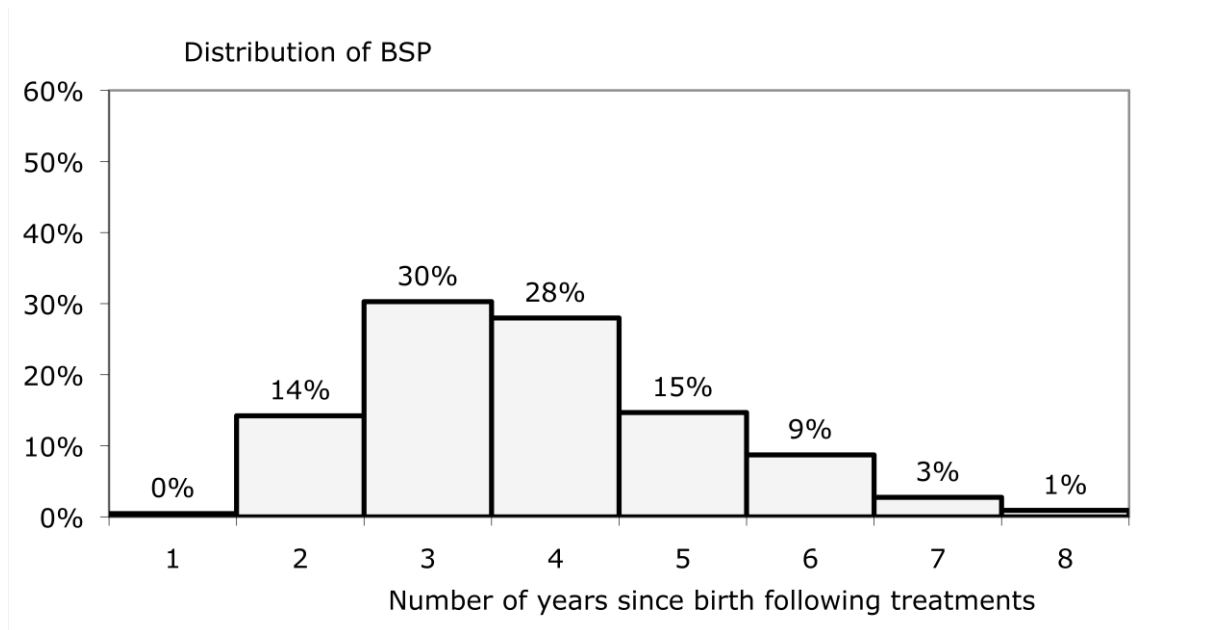


Figure 2. Distribution of BSP over time since last IVF attempt in the inclusion center among unsuccessfully treated couples (n = 193)

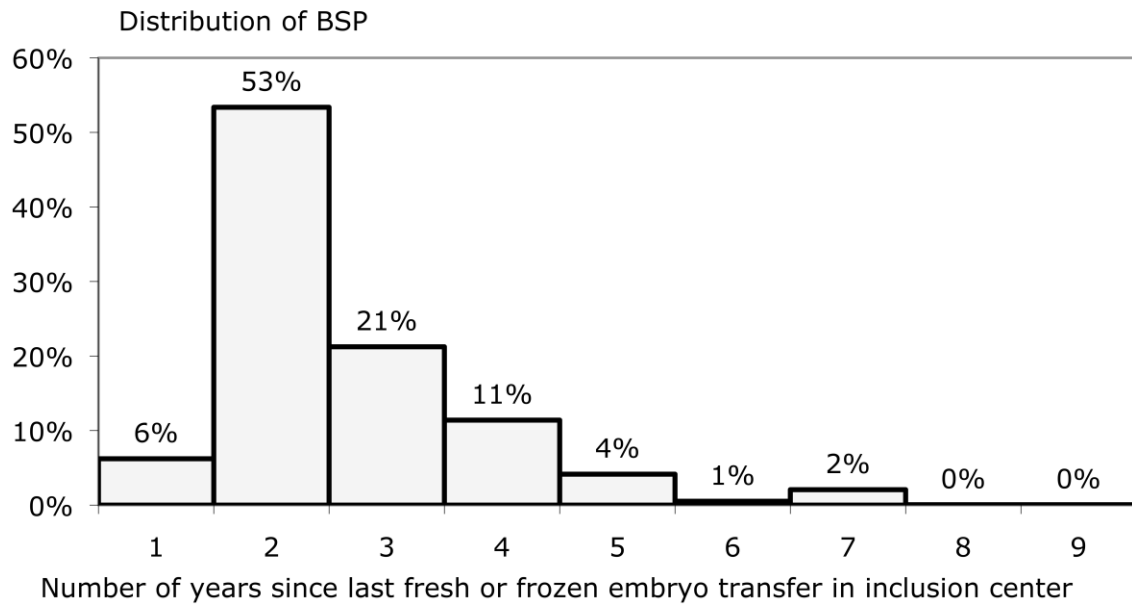


Table 1. Live births following spontaneous conception (BSP) and characteristics of successfully treated couples (n = 1,320) and unsuccessfully treated couples (n = 814).

	Successfully treated couples (n = 1,320)		Unsuccessfully treated couples (n = 814)	
	% BSP	<i>P</i>	% BSP	<i>P</i>
Woman's age at 1st attempt (years)		<0.001		< 0.001
< 30	21.5		41.5	
30-34	18.3		27.4	
35-39	8.3		16.0	
≥ 40	7.1		12.6	
Man's age at 1st attempt (years)		<0.001		0.001
< 30	20.7		26.2	
30-34	21.2		30.7	
35-39	11.6		21.6	
≥ 40	9.1		15.7	
Highest educational level of the couple		0.445		0.782
< French high school diploma	14.6		25.3	
French high school diploma	15.7		21.4	
> French high school diploma	17.6		24.0	
Duration of infertility (years)		0.951		<0.001
0-3	17.1		30.0	
4-5	16.3		25.1	
>5	16.8		9.9	
Type of infertility		0.193		0.346
Primary	16.2		23.6	
Secondary	20.1		27.3	
Origin of infertility		0.001		0.038
Male	12.8		19.3	
Female	17.7		26.6	
Mixed	15.6		19.7	
Unexplained	25.9		31.6	
Previous child before IVF in inclusion center		0.218		0.789
No	17.0		2.9	
Yes	13.1		22.8	
IVF technique at 1st IVF attempt		0.002		0.034
FIV	19.3		26.8	
ICSI	13.0		20.1	
Oocytes retrieved at 1st IVF attempt		0.277		0.425
0-6	13.9		22.0	
7-15	18.0		23.7	
16-40	16.1		28.3	

Embryos transferred at 1st IVF attempt		0.113		0.009
0-1	17.6		20.8	
2	17.9		28.6	
3-5	12.5		17.9	
Number of IVF attempts in inclusion center		0.016		0.001
1	20.3		31.8	
2-4	15.0		22.5	
5-14	11.4		12.4	
Number of frozen embryo transfers in inclusion center		0.018		0.598
0	18.2		23.3	
≥ 1	13.1		25.1	
At least one embryo transferred in inclusion center		0.302		0.059
No*	6.7		14.1	
Yes	16.6		24.5	

* Couples may have been successfully treated in the center or subsequently treated in another center: 15 couples who had no embryo transferred in the inclusion center were later successfully treated elsewhere.

Table 2. Factors associated with live births following spontaneous pregnancy in successfully and unsuccessfully treated infertile couples.

	Successfully treated couples (n = 1,320)							Unsuccessfully treated couples (n = 814)						
	Univariate analysis				Multivariate analysis ^a (n = 1,276)			Univariate analysis				Multivariate analysis ^a (n = 787)		
	n	OR	95% CI	P	OR	95% CI	P	n	OR	95% CI	P	OR	95% CI	P
Woman's age at 1st attempt (years)														
< 30	79/368	1		<0.01 ^b	1		<0.01 ^b	49/118	1		<0.01 ^b	1		<0.01 ^b
30-34	111/607	0.82	0.59-1.13		0.75	0.53-1.07		87/317	0.53	0.34-0.83		0.50	0.31-0.82	
35-39	25/302	0.33	0.20-0.53		0.30	0.18-0.49		43/268	0.27	0.17-0.44		0.24	0.14-0.43	
≥ 40	3/42	0.28	0.08-0.93		0.25	0.07-0.86		14/111	0.20	0.10-0.40		0.18	0.09-0.38	
Duration of infertility (years)				0.85			0.84				<0.01 ^b			<0.01 ^b
0-3	116/679	1			1			102/343	1			1		
4-5	66/405	0.94	0.68-1.32		0.88	0.62-1.26		71/282	0.80	0.56-1.13		0.79	0.54-1.17	
>5	33/196	0.98	0.64-1.50		1.01	0.64-1.59		16/170	0.25	0.14-0.43		0.25	0.14-0.46	
Origin of infertility				<0.01			<0.01				<0.01			<0.01
Male	62/483	1			1			44/228	1			1		
Female	74/419	1.46	1.01-2.10		1.55	1.05-2.30		92/346	1.51	1.01-2.27		1.75	1.09-2.79	
Mixed	38/244	1.25	0.81-1.94		1.16	0.73-1.84		27/137	1.03	0.60-1.75		1.04	0.57-1.88	
Unexplained	44/170	2.37	1.54-3.66		2.55	1.59-4.08		30/95	1.93	1.12-3.32		2.98	1.60-5.53	
Number of attempts in inclusion center				<0.01 ^b			<0.01 ^b				<0.01 ^b			<0.01 ^b
1	94/464	1			1			68/214	1			1		
2-4	110/732	0.69	0.51-0.94		0.65	0.47-0.89		113/503	0.62	0.44-0.89		0.39	0.26-0.60	
5-14	14/123	0.51	0.28-0.92		0.44	0.23-0.82		12/97	0.30	0.16-0.59		0.15	0.07-0.32	
At least one embryo transferred in inclusion center														
Yes	217/1305	1			1			184/750	1			1		
No	1/15	0.36	0.05-2.74	0.32	0.24	0.03-1.98	0.19	9/64	0.50	0.24-1.04	0.06	0.31	0.13-0.70	<0.01
Previous child before IVF														
No	197/1160	1			1			165/691	1			1		
Yes	21/160	0.74	0.46-1.20	0.22	0.81	0.46-1.40	0.45	28/123	0.94	0.59-1.48	0.79	1.03	0.60-1.79	0.91

^a Adjusted for inclusion center; ^b p for trend