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Fertility of Women Treated during Childhood with Triptorelin (Depot Formulation) for Central Precocious Puberty: The PREFER Study

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Abstract
Background: Gonadotropin-releasing hormone analogues (GnRHa) administered as depot formulations are the standard of care for children with central precocious puberty (CPP). Puberty resumes after treatment discontinuation, but little is known concerning fertility in women who have been treated with GnRHa for CPP during childhood. ***Methods:*** The PREFER (PREcocious puberty, FERtility) study prospectively analysed fertility, via a series of questionnaires, in women treated during childhood with triptorelin (depot formulation) for CPP. Co-primary endpoints were the proportion of women wanting a pregnancy any time before study inclusion and during the follow-up period but not pregnant 6 and 12 months after stopping contraception and the waiting time to pregnancy (WTP). ***Results:*** A total of 574 women were identified, and 194 women were included in the analysis. Although there were not enough data for primary endpoint assessment, few women (1.7%) reported issues with fertility or were unable to become pregnant despite trying to conceive. Most pregnancies (84.4%, 95% CI [67.2–94.7%]) occurred within 1 year of trying to conceive, in line with the WTP for women without previous CPP. ***Conclusion:*** The results, based on a limited sample of patients, suggest that CPP treated with triptorelin does not negatively impact women's fertility in adulthood. These results need to be consolidated with a subsequent study performed when these women will have reached their mid-thirties.

Introduction

Precocious puberty (PP) is generally defined as the appearance of the first signs of puberty (breast development in girls and testis enlargement in boys) before the age of 8 years for girls or 9 years for boys [1, 2]. PP can be sub-

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divided into gonadotropin-releasing hormone (GnRH)-dependent and -independent causes. GnRH-dependent PP, also called central precocious puberty (CPP), is due to the early activation of the hypothalamus-pituitary-gonadal axis [3]. Treatment with long-acting GnRH analogues (GnRHa) is the standard of care in children with CPP [4–12]. GnRHa desensitise the pituitary gonadotropic cells to GnRH [13] and decrease FSH and LH secretion and gonadal activation. Their short-term effects on pubertal development are well documented. Long-term effects have been reviewed, but their evaluation is limited by the lack of randomized controlled trials [5, 12].

Discontinuation of GnRHa results in the resumption of puberty [14–16] and in a short post-treatment growth spurt [17–21]. In girls, menarche occurs on average 1 year after treatment discontinuation [17, 22, 23]. There are relatively few data on gonadal function in adolescents and adult women who have been treated for CPP. An increased frequency of signs and symptoms of polycystic ovarian syndrome has been observed in women who had CPP, with potential consequences on fertility, but this remains controversial [5, 12].

The influence of CPP and/or its treatment on reproductive functions is an essential endpoint and is a frequent question asked by parents when GnRHa treatment is discussed. A review of the literature reported that among >100 pregnancies reported in 9 studies in women treated for CPP, there were 97 uneventful pregnancies resulting in healthy children, 5 elective abortions, and 11 early miscarriages [12]. Moreover, the rate of spontaneous pregnancy seems similar between women who have previously been treated with GnRHa for CPP (90.4%; n = 135) and women who did not have CPP during childhood (93.4%; n = 446) [24]. Nevertheless, few large-cohort studies have been published investigating the long-term impact of GnRHa treatment for CPP on fertility in women.

The PREFER (PREcocious puberty, FERtility) study prospectively analysed fertility in a large cohort of women treated during childhood with triptorelin (depot formulation) for CPP. The questionnaire-based study was conducted in France, and the results were compared to those of the general French population.

Methods

The PREFER study was a longitudinal, descriptive, non-comparative, epidemiological study of women treated during childhood with the GnRHa triptorelin (depot formulation; 28-day formulation [3 mg]) for CPP. The study was conducted in 27 centres in France between February 2007 and November 2009. Approval from the French Advisory Committee on the Processing of Information for Medical Research (CCTIRS) was received on June 21, 2006. Approval from the French Data Protection Authority (CNIL) was received on November 3, 2006. The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before enrolment in the study.

Participants

Participants were women aged ≥18 years in 2006 (born in 1988 or earlier) who had been treated during childhood with triptorelin (depot formulation) for idiopathic CPP and had initiated triptorelin therapy between 1984 and 1996. Exclusion criteria were CPP secondary to a peripheral production of androgens or oestrogens (e.g., adrenal hyperplasia or gonadal disorder), CPP of neoplastic origin (except hamartomas), and chromosomal abnormality. Women with CPP associated with adoption were included in the study. Enrolling clinical centres identified potential participants by reviewing archives and checking clinical files against the study inclusion criteria to confirm eligibility.

Study Design

The PREFER study examined fertility in women retrospectively during the 2 years before inclusion and prospectively during a 12-month post-inclusion follow-up period. The primary objective was to analyse the fertility of women treated during childhood with triptorelin (monthly depot formulation) for CPP. Fertility was assessed via a series of questionnaires completed by the women. Secondary objectives were to assess the progress and outcome of any pregnancy, ovarian function and biometrics, concomitant description of fertility with the aetiology of PP and its treatment (duration of GnRHa therapy) or any other medical intervention that might have affected puberty (surgery and other additional treatments), and the socioeconomic consequences of CPP (academic level, relationship status, and occupation).

Assessments

A medical questionnaire was completed by participating centres to gather the following data: chronological age, bone age and Tanner stage at the time of diagnosis and treatment of CPP, GnRH stimulation test results, pelvic ultrasound results, and treatments used (GnRHa therapy and other additional treatments, if applicable). Women were contacted, and their agreement to participate was obtained with a signed informed consent form. Women who agreed to participate completed an inclusion questionnaire on their sociodemographic and fertility status. Follow-up questionnaires were sent to participants 6 months and 12 months after inclusion to assess fertility, pregnancy status, and the outcomes of any pregnancy (see online suppl. Table 1; see www.karger.com/doi/10.1159/000513702 for all online suppl. material).

Endpoints

Co-primary endpoints were the proportion of women desiring pregnancy any time before inclusion and during the follow-up period but not pregnant at 6 and 12 months and the waiting time to pregnancy (WTP: time between attempting to conceive and be-

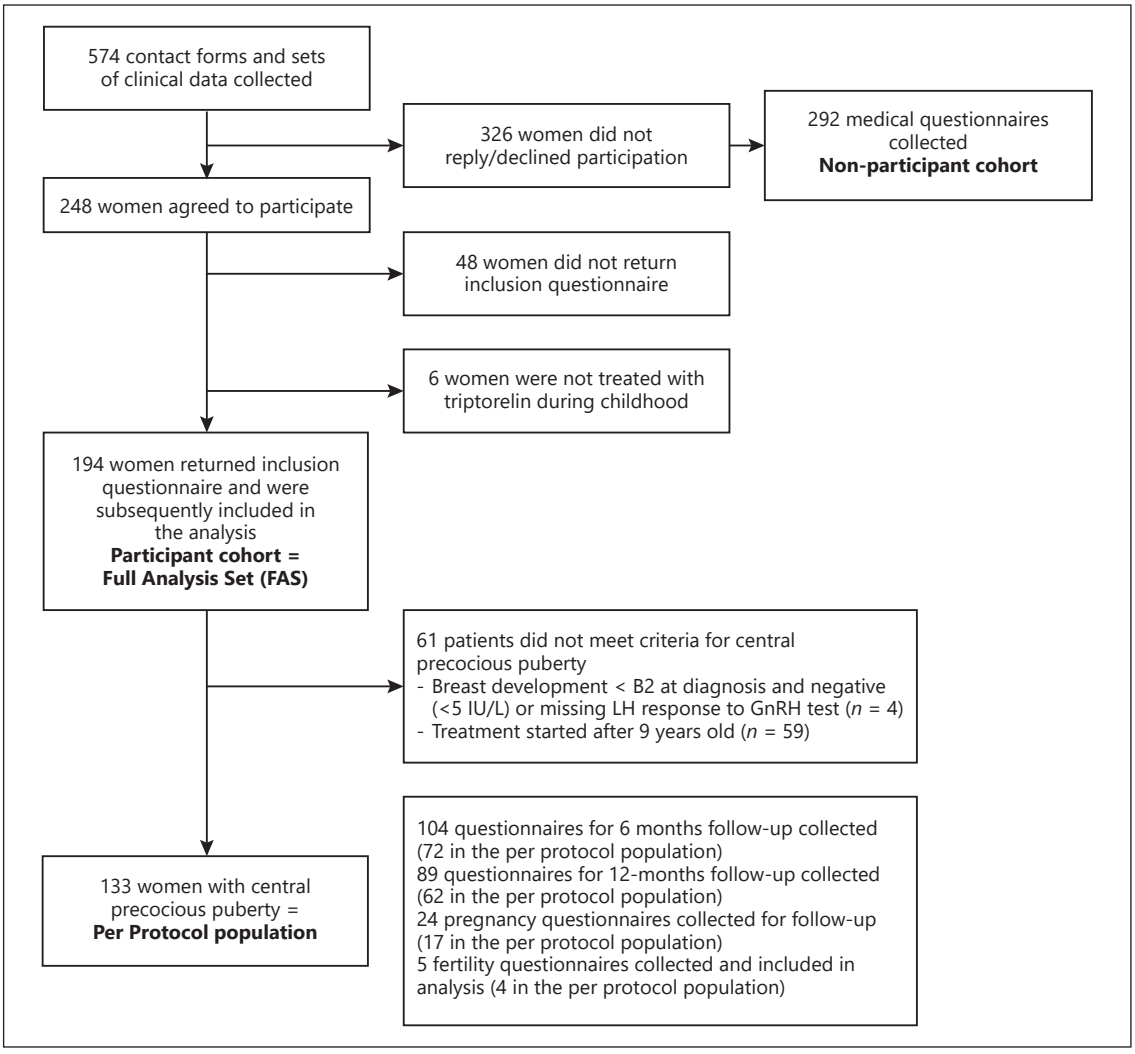

Fig. 1. PREFER study flowchart. FAS, full analysis set; GnRH, gonadotropin-releasing hormone; CPP, central precocious puberty.

coming pregnant) before inclusion. Secondary endpoints (collected at inclusion, 6 months, and 12 months) were the proportion of consultations for infertility or diagnosis of infertility (attempting to conceive for 1 year and no pregnancy or diagnosed during a consultation with a physician) during the 2 years prior to inclusion or during the follow-up period, proportion of unplanned pregnancies prior to the onset of the study, proportion of previous pregnancies and the difficulty in achieving them, proportion of spontaneous abortions and ectopic pregnancies, and the mode of delivery for pregnancies. Only the first pregnancy was considered for all endpoints. Other secondary endpoint data collected at inclusion were age at puberty (defined by onset of menarche), regularity and length of menstrual cycles and menstrual irregularities, current height, weight, and BMI, smoking status, academic level, occupation, and relationship status.

Sample Size and Statistical Analysis

The sample size needed to determine the 1-year pregnancy rate in women was 162. This was based on a 1-year pregnancy rate in the general population of 85% of women attempting pregnancy [25], with a 10% precision rate, an alpha risk of 0.05, and 15% loss of participants to follow-up. Taking into account the age distribution of mothers at the time they give birth [26] and the age distribution of women in France [27], it can be calculated that approximately 27% of women aged 18–30 years will give birth within a 3-year period. Based on these assumptions, a target of 597 patients was set for this study. Assuming that 60% of the patients contacted would be willing to participate (as shown in the feasibility study), 995 women treated for CPP needed to be contacted. Checks for population biases were performed by comparing data (height, weight, chronological age, statural age, bone age, Tanner stage, and proportion of patients with menses) at diagnosis and at the start and end of triptorelin treatment collected from partici-

Table 1. Clinical characteristics of PP in participants and non-participants

Variable	Participants				Non-participants	
	FAS population		per protocol population			
	mean ± SD (range)	*N*	mean ± SD (range)	*N*	mean ± SD*	*N*
Age at diagnosis of CPP, years	8.0±1.5 (1.5–11.3)	186	7.5±1.5 (1.5–9)	129	7.6±1.5	292
Age at initiation of triptorelin therapy, years	8.3±1.4 (1.5–11.3)	178	7.8±1.4 (1.5–9)	122	7.9±1.5	292
Height at initiation of triptorelin therapy, cm	132.7±9.3 (87.5–153.5)	182	130.9±9.8 (87.5–150)	124	132.6±10.7	292
Bone age at initiation of triptorelin therapy, years	10.2±1.5 (3.5–13)	162	9.8±1.6 (3.5–12)	109	10.1±1.6	292
Breast development at initiation of triptorelin (Tanner stage)		165		110		237
B1	2.4%	4	1.8%	2[$]	0%	0
B2	43%	71	37.3%	41	45.6%	108
B3	47.9%	79	55.5%	61	46.4%	110
B4–5	6.7%	11	5.4%	6	8.0%	19
Pubic hair development at initiation of triptorelin (Tanner stage)		173		118		249
P1	25.4%	44	27.1%	32	19.7%	49
P2	48%	83	49.2%	58	55.4%	138
P3	22%	38	21.2%	25	20.9%	52
P4–5	4.6%	8	2.5%	3	4.0%	10
Age at end of triptorelin therapy, years	10.6±0.9 (3.4–12.8)	177	10.4±1.0 (3.4–12.8)	121	10.3±1.2	292
Duration of triptorelin therapy, years	2.4±1.2 (0.5–8.6)	181	2.7±1.3 (0.5–8.6)	124	na	–
Bone age at the end of triptorelin treatment, years	11.7±1.0 (3.5–13.5)	165	11.7±1.1 (3.5–13.5)	111	11.4±1.1	292
Age at menarche, years	11.8±1.4 (7.0–16.0)	174	11.6±1.4 (7.0–16.0)	119	na	–

PP, precocious puberty; na, not available; CPP, central precocious puberty; FAS, full analysis set. * No range was available for the non-participants' data.
[$] Two women with Tanner stage B1 were included since they had a peak LH level >5 IU/L.

pants' medical records and also from women who did not reply or declined participation in the study. Data from the questionnaires were entered into an electronic database. However, given the difficulties in retrieving old patient records and chart data, only minimal data monitoring could be performed. Qualitative variables were presented using number of missing data, frequency, and percentage; quantitative variables were presented using frequency of missing and non-missing values, mean, standard deviation, and range (minimum and maximum). Binomial 95% confidence intervals (CI) were computed for proportions. Statistical analysis was performed using SAS® software (v9.4). Inconsistent data were discarded. During the analysis, 2 population of patients were considered, a full analysis set (FAS) population including all participants and a per protocol population excluding patients who did not respect the criteria for CPP, in particular in terms of age at onset (initiating treatment after the age of 9 years, considering a maximum of 1 year between onset and start of treatment), pubertal development (absence of breast development), and GnRH test results (prepubertal) (Fig. 1). A clinical study report was produced in September 2015 and was the basis for an earlier version of this manuscript. However, during the review process, a number of inconsistencies in the analysis were highlighted. Therefore, data analysis was resumed in 2019–2020. The current manuscript and an updated version of the clinical study report are based on this new analysis of the data that had been collected in 2007–2009. The study was approved by the "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé" on July 21, 2006 (#06.118), and by the "Commission nationale de l'informatique et des libertés" on November 3, 2006 (#906229).

Results

Participants

Overall, 574 women meeting the inclusion criteria were identified at 27 centres in France between February 2007 and November 2009 (Fig. 1; Table 1). There were 3–97 women per centre and 248 accepted to participate (43%, 0–62% for each centre, median 41%), with a final cohort of 194 women included (FAS population) and 133 women in the per protocol population. The clinical characteristics of participants were very similar to those who did not participate (Table 1). The mean age of participants at study inclusion was approximately 24 years, and their self-reported social characteristics and gynaecological history are presented in Table 2. It is noteworthy that the mean height (162 cm) was close to the national average height (163 cm) [28], and that >50% of participants aged ≥25 years had completed full-length higher education programmes (online suppl. Table 2).

Table 2. Characteristics of participants at inclusion (FAS population and per protocol population)

Variable	FAS population		Per protocol population	
	mean ± SD (range)[a]	*N*[b]	mean ± SD (range)[a]	*N*[b]
Age at inclusion, years	24.3±3.0 (18.4–33.3)	187/194	24.3±3.1 (18.4–30.8)	128/133
Proportion with regular menstrual cycles, *n* (%)	126 (68.1)	185/194	86 (67.7)	127/133
Cycle length, days	28.4±1.7 (24–34)	86/126[c]	28.3±1.5 (26–33)	65/86[c]
Age at first sexual intercourse, years	17.5±2.2 (14.0–26.0)	167/173[d]	17.4±2.3 (14.0–26.0)	114/117[d]
Height, cm	161.6±6.1 (145.0–178.0)	188/194	161.9±6.3 (145–178)	128/133
Weight, kg	61.1±13.1 (40.0–147.0)	185/194	61.7±13.6 (43–147)	126/133
BMI, kg/m^2	23.4±4.8 (15.9–50.9)	184/194	23.5±4.8 (15.9–50.9)	125/133
Smoking status, *n* (%)		188/194		128/133
Current smoker	54 (28.7)		37 (28.9)	
Former smoker	23 (12.2)		9 (7.0)	
Non-smoker	111 (59.0)		82 (64.1)	
In a relationship, *n* (%)	123 (68.3)	180/194	81 (66.4)	122/133
Live together	79 (65.3)	121/123[e]	48 (60.8)	79/81[e]
Do not live together	42 (34.7)	121/123[e]	31 (39.2)	79/81[e]
Not in a relationship	57 (31.7)	180/194	41 (33.6)	122/133
Highest academic level, *n* (%)		194		133
None	5 (2.6)		3 (2.3)	
Completed only primary school	1 (0.5)		1 (0.8)	
Completed junior secondary school (up to 15 years)	12 (6.2)		10 (7.6)	
Completed technical college	15 (7.7)		12 (9.0)	
Completed secondary school (baccalaureate)	53 (27.3)		38 (28.6)	
Completed 2-year programme of university studies	28 (14.4)		20 (15.0)	
Achieved full-length university studies	80 (41.2)		49 (36.8)	
Occupation, *n* (%)		192		132
Employed	105 (54.7)		76 (57.6)	
Student or in training	67 (34.9)		44 (33.4)	
Housewife/not working	7 (3.6)		4 (3.0)	
Unemployed	13 (6.8)		8 (6.1)	
Professional category for those employed,[f] *n* (%)		124		87
Employee	78 (62.9)		55 (63.2)	
Senior executive	22 (17.7)		16 (18.4)	
Middle management employee	18 (14.5)		12 (13.8)	
Farmer	2 (1.6)		1 (1.1)	
Self-employed/freelancer	3 (2.4)		2 (2.3)	
Tradeswoman	1 (0.8)		1 (1.1)	

FAS, full analysis set; CPP, central precocious puberty; SD, standard deviation. [a] Unless otherwise stated. [b] Due to the nature of the study, data are not available for all participants for each parameter, and thus the number of participants for which the parameter was available is indicated. [c] Number of women with regular menstrual cycle. [d] Number of women that already had first sexual intercourse at study inclusion. [e] Number of women in a relationship. [f] Excludes participants who responded under professional category that they were students or unemployed.

Pregnancy

At inclusion, 142 women in the FAS population (97 in the per protocol population) had never been pregnant (Table 3). Of these women, 85.2% in the FAS population and 85.6% in the per protocol population declared they did not want to become pregnant, and 2.1 and 3.1%, respectively, declared that they had been unable to become pregnant. At inclusion, 43 women in the FAS population (31 in the per protocol population) declared they had been pregnant and 4/42 (9.5%) reported difficulties to conceive (3/30 [10.0%] in the per protocol population). These 43 women in the FAS population reported 62 past pregnancies (30 [69.8%] 1 pregnancy, 9 [20.9%] 2 pregnancies, and 4 [9.3%] 3 or 4 pregnancies). Similar numbers of pregnancies were observed in the per protocol population. During the study, primigravida pregnancies

Table 3. Participants' desire for pregnancy and pregnancy outcomes before inclusion in the study

Variable	FAS population (N = 194) n (%)	Per protocol population (N = 133) n (%)
Did not want to become pregnant	121/142[a] (85.2)	83/133[a] (85.6)
Unable to become pregnant	3/142[a] (2.1)	3/97[a] (3.1)
Women pregnant prior to inclusion, n	43/194 (22.2)	31/133 (23.3)
Pregnancies prior to inclusion, n	62	46
Wanted	22 (52.4)	16 (53.3)
Unexpected	16 (38.1)	11 (36.7)
Occurred despite using contraception	4 (9.5)	3 (10.0)
Data missing	1	1
Pregnancy outcomes for pregnancies before inclusion or ongoing at time of inclusion	45	32
Delivery	28[b] (62.2)	21[b] (65.6)
Elective abortion	13 (28.9)	8 (25.0)
Abortion for medical reasons[c]	3 (6.7)	2 (6.3)
Miscarriage	1 (2.2)	1 (3.1)

FAS, full analysis set. [a] Denominator is all women never having been pregnant at inclusion in the FAS/per protocol population. [b] Including 1 twin birth. [c] The high number of medical abortions is likely due to a misunderstanding of respondents with elective abortion.

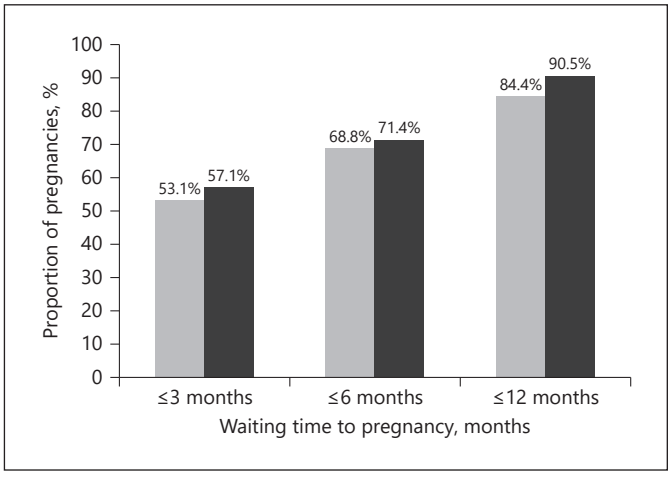

Fig. 2. WTP for pregnancies occurring before inclusion in the PREFER study. The proportion of women with various WTP is represented for the pregnancies with this information available in the FAS population (n = 32, black boxes) and in the per protocol population (n = 21, grey boxes). WTP, waiting time to pregnancy; FAS, full analysis set.

were reported by 6 women at inclusion, 4 at 6 months, and 2 at 12 months of follow-up in the FAS population. Therefore, at least 55/194 (28.4%) participants (37/133 [27.8%] in the per protocol population) had at least 1 pregnancy before or during study follow-up. WTP was available for 32 pregnancies that occurred prior to inclusion in the study and 21 pregnancies in the per protocol population and showed that a pregnancy was achieved within 12 months for 27/32 (84.4%) women (95% CI [67.2–94.7%]) in the FAS population and 19/21 (90.5%) women in the per protocol population (95% CI [69.6–98.8%]) (Fig. 2).

Fertility

At 6 and 12 months in the study, 78/92 (84.8%) and 66/73 (90.4%), respectively, of participants in the FAS population reported using contraception, therefore limiting the number of patients who were eligible for the infertility and pregnancy questionnaires. At inclusion in the study, among the women in the FAS population with available data, 1/132 (0.8%) reported having a fertility problem, 25/132 (18.9%) reported having no fertility problem, 35/132 (26.5%) did not know whether they had a fertility problem, and 71/132 (53.8%) felt that the question did not apply to them. Results were similar in the per protocol population. Three women had sought advice for infertility before participation in the study, 1 of whom had also reported having a fertility problem.

At 6 months and 12 months in the study, 5/85 (5.9%) and 0/52, respectively, of the participants in the FAS population had consulted a physician during the previous 6 months for difficulties in conceiving. Finally, among the women in the FAS population who had stopped contra-

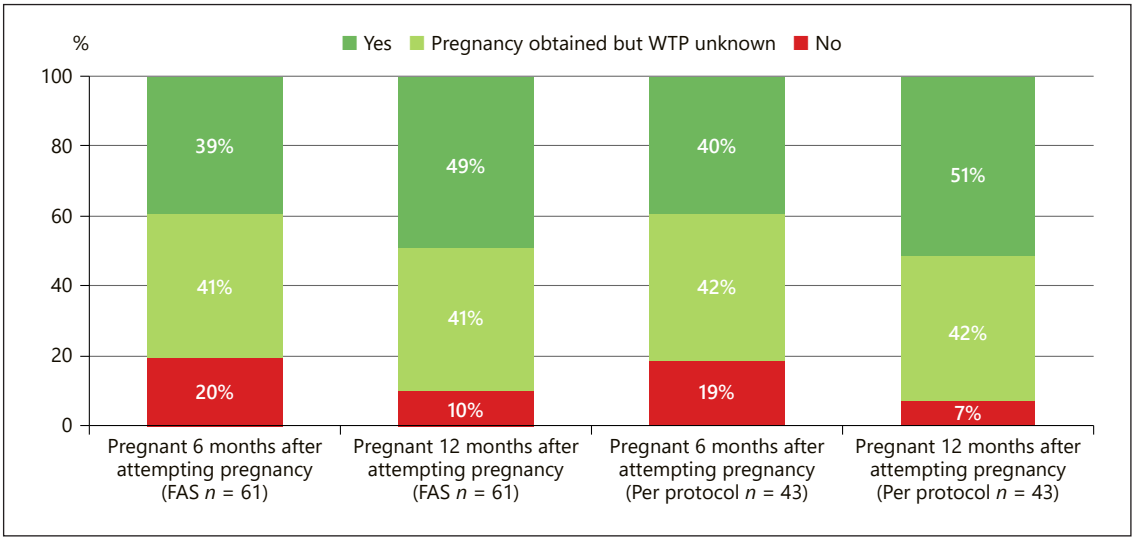

Fig. 3. Proportion of women with pregnancy among those desiring pregnancy 6 and 12 months after having stopped contraception methods. The analysis was performed on women pregnant at least once or trying to get pregnant and having stopped all contraception methods. Modality "unknown" concerns women with unexpected pregnancies or missing dates to calculate WTP. All pregnancies or pregnancy attempts were considered including those before the study, at study inclusion, and at 6-month and 12-month follow-up. WTP, waiting time to pregnancy; FAS, full analysis set.

ception and were trying to conceive during the study, 12/61 (19.7%) and 6/61 (9.8%) were not pregnant after attempting pregnancy for 6 and 12 months, respectively (Fig. 3).

Discussion

In the PREFER study, few (1.7%) women reported problems with fertility or were unable to become pregnant despite trying to conceive. Most pregnancies (84.4%, 95% CI [67.2–94.7%]) in the PREFER study cohort occurred within 1 year of trying to conceive, and the 12-month WTP was similar to that previously published for women without CPP trying to conceive (~85%) [25, 29–31]. Most women who had not been pregnant up to the day of inclusion or during the study declared they did not want a pregnancy. Our results support those from previous studies in patients treated during childhood with GnRHa for CPP [24, 32, 33] and highlight the fact that fertility outcomes are better evaluated in women in their late 20s than mid-20s, given the median age of 28 years at first pregnancy in France 2007 (INED) [34].

The proportion of women who reported a fertility problem in our study (1.7%) was particularly low and needs to be compared with results from other similar studies and from the general population. Lazar et al. [24] reported higher prevalence of fertility problems of 11.1 and 10.9% of women who had received triptorelin treatment for CPP or early puberty, respectively. In the general population, an international review of 25 population surveys sampling 172,413 women reported a median prevalence of infertility of 9% [35]. In a US cross-sectional cohort study of 4,558 women, 623 (13.7%) and 328 (7.2%) reported seeking an infertility evaluation and undergoing subsequent infertility treatment, respectively [36]. The younger age of the population included in the PREFER study (mean 24 years) compared with the Lazar study (mean 33 years) could have contributed to these differences; moreover, fertility mostly declines after the age of 35 years [37].

Interestingly, the PREFER study participants had a higher level of education than expected in the general population, which possibly had an influence on the study results. Over half of the respondents who were 25 years or over had completed full-length higher education programmes, compared with only 18% of 25- to 49-year old women in the general population in France [38]. The proportion of women with an occupation was higher in the PREFER study than in the French general population. There were more senior management executives, employees, and students and less inactive persons in the PREFER study population than in the general population [38]. This may result from selection

biases, either from increased awareness of CPP in families with a higher level of education or from increased willingness to complete the questionnaire in those with a higher educational/professional status. In contrast, Lazar et al. [24] reported that the educational level of women with CPP (whether treated or untreated) was similar to that of the general population. In addition, early puberty in general (i.e., not associated with CPP per se) has been reported to detrimentally affect academic performance and subsequent academic achievement, including the lesser likelihood of pursuing a college education and the tendency to be employed in lower-paying, less prestigious jobs [39]. Although the design of the PREFER study does not allow us to explain why its patient population has such a high level of education, it is clear that this affects our analysis of fertility in this cohort, given the association between age at first pregnancy and level of education with a mean of 29 years for high versus 26 years for intermediate and 24 years for low educational levels in France [40].

The PREFER study has several limitations. The primary objective was to analyse prospectively the fertility of women treated during childhood with triptorelin (depot formulation) for CPP. However, once all the questionnaires had been collected, there were insufficient data to conclude on the primary endpoint (i.e., the proportion of women desiring a pregnancy but not pregnant 6 and 12 months after having stopped all contraception methods). Therefore, the proportion of women achieving pregnancy after 12 months (84.4%) was calculated on a small sample of 32 pregnancies leading to wide confidence intervals (95% CI [67.2–94.7%]). The design of the questionnaires also meant that certain parameters could not be fully documented (e.g., although data on total number of pregnancies were collected, most detailed information was collected on a maximum of 3 pregnancies per woman, but some women were pregnant >3 times). Consequently, some planned analyses could not be performed, and some aberrant values were discarded. Data that could not be presented were duration of pregnancy, distribution of birth weight and sex ratio, rate of preterm births and macrosomy, rate of stillbirths and birth defects, episodes of amenorrhoea or menstrual irregularities, acne and body hair, hormonal treatments initiated before or since puberty, hormone monitoring and abnormal hormone levels, characterisation of CPP, any episodes of triptorelin treatment suspension, and concomitant treatments.

In addition, a high proportion of patients declined to participate or did not respond to the invitation to participate. We were able to compare height, weight, chronological age, bone age, and Tanner stage at the time of diagnosis of CPP and at the beginning and end of treatment with triptorelin for the 292 non-participants and the 194 women included in the study. No statistically significant difference was found between participants and non-participants. While this suggests that there was no selection bias based on these parameters, the educational status of women differed, however, between the PREFER study cohort and populations in other studies and in the general population. This may have resulted from patient- or centre-selection bias. Nevertheless, the method of data collection in the PREFER study allowed a large cohort to be studied with the use of standardized questionnaires.

Conclusion

The PREFER study showed that the WTP and pregnancy rate for women treated during childhood with triptorelin (depot formulation) for CPP was consistent with that reported for the general population in France, although with a wide confidence interval. Women in the PREFER study cohort had a low prevalence of infertility. These results, based on a limited sample of patients, suggest that CPP treated during childhood with the GnRHa triptorelin does not negatively impact women's fertility in adulthood. Given the age profile of the PREFER cohort, these results need to be consolidated with a subsequent study performed 10 years later to assess, retrospectively, fertility and infertility rates when these women will have reached their mid-thirties.

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Statement of Ethics

The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before enrolment in the study. Approval for use of medical records and data was obtained from the French Advisory Committee on the Processing of Information for Medical Research (CCTIRS) and the French Data Protection Authority (CNIL).

Conflict of Interest Statement

Jean-Claude Carel is a co-ordinating investigator for a study sponsored by Ipsen Pharma. Jacques de Mouzon had a contract as a scientific advisor for Ipsen Pharma, performed the statistical analyses, and created a study report for the initial PREFER study. Laetitia Martinerie has received lecture fees from Ipsen Pharma and has been invited by Ipsen Pharma to attend international scientific meetings. Joelle Blumberg, Luigi di Nicola, and Pascal Maisonobe are present or former employees of Ipsen Pharma.

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