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CASE REPORT

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# Idiopathic central precocious puberty in a Klinefelter patient: highlights on gonadotropin levels and pathophysiology

Salwan Maqdasy<sup>1,2,3\*</sup>, Bertrand Barres<sup>4</sup>, Gaele Salaun<sup>5</sup>, Marie Batisse-Lignier<sup>1</sup>, Celine Pebrel-Richard<sup>5</sup>, Kelvin H. M. Kwok<sup>6</sup>, André Labbé<sup>7</sup>, Philippe Touraine<sup>8</sup>, Florence Brugnon<sup>2,9,10</sup> and Igor Tauveron<sup>1,2,3</sup>

## Abstract

**Background:** Idiopathic central precocious puberty (ICPP) is supposed to be non-existent in a context of testicular destruction that is typically present in Klinefelter syndrome (KS). Herein, we describe a rare case of ICPP in a Klinefelter patient (47,XXY) with 2 maternal X chromosomes. Moreover, we highlight the differences in gonadotropin levels in comparison to males with ICPP and a normal karyotype.

**Case presentation:** An 8 years old boy with a history of cryptorchidism was evaluated for precocious puberty (Tanner staging: P2/G3). Both testes measured 25x35mm. His hormonal profile confirmed a central origin of precocious puberty with high serum testosterone (4.3 ng/ml), luteinizing hormone [LH (3.5 UI/l)] and follicle stimulating hormone [FSH (7.7 UI/l)] levels. Luteinizing hormone-releasing hormone (LHRH) test amplified LH and FSH secretion to 24 and 14 UI/l respectively. Brain magnetic resonance imaging (MRI) was normal. No MKRN3 mutation was detected. He was treated for ICPP for two years. During puberty, he suffered from hypergonadotropic hypogonadism leading to the diagnosis of KS (47,XXY karyotype). Chromosomal analysis by fluorescent multiplex polymerase chain reaction (PCR) using X chromosome microsatellite markers identified 2 maternal X chromosomes. Analysing 8 cases of KS developing ICPP (our reported case and 7 other published cases) revealed that these KS patients with ICPP have higher LH and FSH levels during ICPP episode than in ICPP patients with a normal karyotype (ICPP with KS vs ICPP with a normal karyotype: LH levels  $9.4 \pm 12$  vs  $1.1 \pm 0.6$  UI/l; FSH levels  $23.1 \pm 38.5$  vs  $2.7 \pm 1.5$  UI/l). Furthermore, their response to gonadotropin-releasing hormone (GnRH) stimulation is characterized by excessive LH and FSH secretion (LH levels post-GnRH:  $58 \pm 48$  vs  $15.5 \pm 0.8$  UI/l; FSH levels post-GnRH:  $49.1 \pm 62.1$  vs  $5.7 \pm 3.9$  UI/l).

**Conclusions:** ICPP in boys is extremely rare. The pathophysiology of ICPP in KS is unknown. However, maternal X supplementary chromosome and early testicular destruction may play a significant role in the initiation of ICPP, in part explaining the relative "overrepresentation" of ICPP in KS. Thus, karyotype analysis could be considered for boys suffering from ICPP, especially if testicular size is smaller or gonadotropins are significantly elevated.

**Keywords:** Precocious puberty, Idiopathic, Klinefelter, Gonadotropin

\* Correspondence: [smaqdasy@chu-clermontferrand.fr](mailto:smaqdasy@chu-clermontferrand.fr)

<sup>1</sup>CHU Clermont-Ferrand, Service d'endocrinologie, diabétologie et maladies métaboliques, 58, rue Montalembert, F-63003 Clermont-Ferrand, France

<sup>2</sup>Université Clermont Auvergne, Faculté de médecine, F-63003 Clermont-Ferrand, France

Full list of author information is available at the end of the article



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## Résumé

**Introduction:** Une puberté précoce centrale idiopathique (PPCI) est extrêmement rare chez le garçon. Sa prévalence chez les garçons présentant un syndrome de Klinefelter (SK) est méconnue. Nous décrivons un cas rare de PPCI chez un garçon présentant un SK (47,XXY). De plus, nous surlignons les différences observées entre les taux de gonadotrophines en cas de PPCI chez les patients avec caryotype normal ou présentant un syndrome de Klinefelter.

**Cas clinique:** Un garçon de 8 ans avec des antécédents de cryptorchidie a été pris en charge pour une puberté précoce (PP) (Stade de *Tanner*: P2/G3). Les diamètres des testicules étaient élevés pour son âge (25x35mm pour chaque côté). Le bilan hormonal a confirmé une PP avec des concentrations sanguines de testostérone, LH et FSH élevées à 4.3 ng/ml, 3.5 UI/l et 7.7 UI/l respectivement. Un test à la LHRH a révélé une réserve très élevée de LH (24 UI/l) et de FSH (14 UI/l). Aucune lésion tumorale n'a été mise en évidence par l'IRM. La recherche de mutation du gène MKRN3 n'a révélé aucune anomalie. Le garçon a été suivi et pris en charge pour une PPCI durant 2 ans. A la fin de la puberté, un hypogonadisme périphérique a permis d'évoquer le diagnostic de SK (47,XXY). L'analyse chromosomique par PCR en utilisant des marqueurs de chromosome X a confirmé l'origine maternelle des deux chromosomes X.

**Discussion:** À ce jour, 7 cas de PPCI ont été décrits chez des garçons avec un SK. Nous avons analysé les données de ces patients et comparé aux données de patients avec une PPCI mais avec un caryotype normal. Nous mettons en exergue un taux significativement élevé de la LH et de la FSH lors du diagnostic de la PPCI chez les patients avec un SK en comparaison avec un caryotype normal (LH:  $9.4 \pm 12$  vs  $1.1 \pm 0.6$  UI/l; FSH:  $23.1 \pm 38.5$  vs  $2.7 \pm 1.5$  UI/l). De plus, les taux de la LH et FSH après une stimulation par la GnRH étaient également très élevés (LH:  $58 \pm 48$  vs  $15.5 \pm 0.8$  UI/l; FSH:  $49.1 \pm 62.1$  vs  $5.7 \pm 3.9$  UI/l).

**Conclusions:** Une PPCI est extrêmement rare chez le garçon. La description de 8 cas de PPCI dans la littérature indique un surrisque de cette pathologie chez les garçons souffrant d'un SK. La physiopathologie reste méconnue. L'origine maternelle du chromosome surnuméraire et la destruction précoce du testicule en lien avec l'anomalie chromosomique pourraient favoriser une puberté précoce. Ainsi, une analyse du caryotype pourrait être proposée chez un garçon souffrant d'une PPCI.

**Mots clés:** Puberté précoce, idiopathique, Klinefelter, gonadotrophines

## Background

Puberty in boys is initiated when gonadotropin-releasing hormone (GnRH) secretion is amplified, inducing the secretion of gonadotropins. Pulsatile secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is accompanied by enlarged testicular volume, testosterone secretion and initiation of spermatogenesis [1]. The age of puberty initiation is variable across sex, ethnicity, and is influenced by genetic and nutritional factors. Precocious puberty (PP) is generally due to premature sexual steroid secretion [1–4]. In most cases, puberty is considered precocious in boys if it is initiated before 9 years old. The prevalence of PP is about 1 to 8/10000 with a female/male ratio of 9/1. Central precocious puberty (CPP) is caused by earlier pulsatile secretion of GnRH and gonadotropins [2]. Unlike delayed puberty, CPP remains idiopathic in most of the cases (ICPP) [4]. Many observations suggest a possible link between chromosomal anomalies and PP, especially in Klinefelter syndrome (KS) [5–7]. KS is the most frequent dysgonosomia in boys that leads to incomplete puberty and hypergonadotropic hypogonadism [8]. Indeed, most cases of PP in KS arise from germ cell tumors secreting human chorionic gonadotropin (hCG). While

many cases of ICPP in KS have been reported in the literature, [9–14], the physiopathology remains unclear. Furthermore, the hormonal profile of patients with ICPP and KS is not well characterized. The study of patients with divergent problems such as ICPP and KS might improve the understanding of ICPP pathophysiology and point out factors that influence the timing of puberty initiation.

We describe a case of ICPP in a boy who, a few years later, developed hypogonadism in his adulthood secondary to KS (with 2 maternal X chromosomes). In addition to our patient, we analyze 7 other cases of ICPP in KS patients previously reported in the literature. Among patients with ICPP, those who are also suffering from KS have higher levels of gonadotropins and an exaggerated response to GnRH stimulation compared to those with a normal karyotype. This comparison highlights the possibility of a primitive testicular factor, such as precocious germ cell and Leydig cell dysfunction, participating in the induction of ICPP in KS.

## Case presentation

A boy, born in 1994, was evaluated for suspicion of precocious puberty. At 8 years old, his height (150 cm)

exceeded the mean for age by 3 standard deviations with a growth rate of 10 cm per year. He developed puberty signs (Tanner staging: P2/G3). Both testes measured 25x35mm, the penis was enlarged and increased in length. Bone age was advanced (10 years according to modified Sempé's method). His past history was marked by cryptorchidism, operated at age of 1 year. No facial dysmorphism, behavioural abnormalities or mental retardation were noticed.

His hormonal profile confirmed a central origin of precocious puberty with high serum testosterone (4.3 ng/ml) for age, and detectable LH (3.5 UI/l) and FSH (7.7 UI/l) (adult male reference values for FSH: 1.1–9.9 UI/l, and LH: 0.9–6.6 UI/l).

Luteinizing hormone-releasing hormone (LHRH) test amplified LH and FSH secretion to 24 and 14 UI/l respectively (Table 1). Hypothalamic-pituitary MRI was normal. Due to advanced bone age and growth acceleration, he was treated with triptoreline (3 mg, intramuscular injection every 28 days). Under this treatment, LH, FSH and testosterone were attenuated to a prepubertal level (0.2 UI/l, 0.4 UI/l and 0.2 ng/ml respectively) (Table 1). In 2005, the treatment was stopped, and puberty resumed. At age of 20, he consulted for hypogonadism and bilateral gynecomastia. His definitive height was 178 cm (predicted height was 173 cm, with mid-parental height estimated to 166 cm) and his weight was 86 kg (+ 1 SD). The testicular size was reduced (25 × 12 mm). Further evaluation confirmed azoospermia, and low testosterone levels (1.16 ng/ml, reference values for adults > 2.75 ng/ml) with hypergonadotropic hypogonadism (LH and FSH increased to 26 and 40 UI/l respectively) (Table 1). Testicular biopsy revealed a hyalinized tissue with failed spermatozoa retrieval.

Chromosome analysis was performed on GTG-banded and RHG-banded metaphases prepared from cultured peripheral blood according to the standard protocols.

The origin of the supernumerary X chromosome was investigated by fluorescent multiplex polymerase chain reaction (PCR) to study short tandem repeats polymorphisms (supplementary methods).

Peripheral blood cytogenetic analysis of our patient revealed 47 chromosomes, with an extra X chromosome in all analyzed metaphases, confirming KS. Array-comparative genomic hybridization (CGH) excluded the presence of any other genomic imbalance, except for copy number variations (CNV) previously described in the normal population according to the Database of Genomic Variants (<http://projects.tcag.ca/variation>). Microsatellite analysis in X chromosome showed two X chromosomes of maternal origin. Furthermore, no mutation was found in the coding regions of *MKRN3* gene.

An informed written consent was obtained from the patient and his parents to perform the genetic analyses and to accept the publication of the data in this article.

### Literature analysis and discussion

We collected and analyzed clinical and hormonal data in our case and 7 other cases of ICPP in KS reported in the literature [9–14]. The clinical and biological data at definitive puberty in each case were also considered. The characteristics of the 8 cases of ICPP in KS are summarized in Table 2. We also compared the hormonal profile between ICPP patients with KS (8 cases) and those with a normal karyotype reported in the literature (the most comprehensive cohort is published by Pigneur et al. [15]). Compared to patients with a normal karyotype (46,XY), KS patients have significantly higher LH and FSH levels during precocious puberty (KS + ICPP vs normal karyotype+ICPP: LH levels  $9.4 \pm 12$  vs  $1.1 \pm 0.6$  UI/l; FSH levels  $23.1 \pm 38.5$  vs  $2.7 \pm 1.5$  UI/l). Moreover, the response to LHRH in KS patients is more drastic (KS + ICPP vs normal karyotype+ICPP: LH levels post-LHRH  $58 \pm 48$  vs  $15.5 \pm 0.8$  UI/l; FSH levels post-LHRH:  $49.1 \pm 62.1$  vs  $5.7 \pm 3.9$  UI/l) (Table 3). Even higher basal and stimulated- LH and FSH levels during ICPP were noted in a KS patient with 48, XXYY karyotype [12] compared to boys with either normal karyotype [15] or 47,XXY (7 patients) (Table 2).

In our patient, despite the precocious puberty, target height was attained. Similarly, in other reported cases of ICPP with KS, the height was attained in all patients,

**Table 1** Clinical and biological parameters of the patient during and after puberty

Age	8 years	9.5 years	9 years, 10 months	10 years, 4 months	11.5 years	20 years
LH (UI/l)	3.5	0.2	0.2	0.2	0.3	26
FSH (UI/l)	7.7	0.4	0.4	0.4	0.5	39.6
Testosterone (ng/ml)	4.35	0.3	0.2	0.2	0.3	1.16
Testicular diameter (mm)	35 × 25	35 × 20	35 × 20	35 × 20	35 × 20	25 × 12
Tanner staging	P2G3	P2G3	P2G3	P2G3	P3G3	P3G2
Bone age	9 years, 11 months		11 years, 6 months	11 years, 6 months	12 years, 3 months	

LH: luteinizing hormone; FSH: follicle stimulating hormone; UI: International units  
Period of Triptoreline treatment. Reference values: FSH: 1.1–9.9 UI/l, LH: 0.9–6.6 UI/l

**Table 2** Analysis of characteristics of Klinefelter patients with ICPP

Studies	Characteristics during precocious puberty						Final puberty-adulthood				
	Karyotype	Age at PP	LH	LH post LHRH	T	TV	Height (cm)	LH	FSH	T	TV
Leon et al. [9]	Mosaic XY/XXY/XXXY	8	-	-	-	-	173	-	-	-	-
Mühlendahl et al. [10]	47,XXY	8.3	6.3	42	3	3.4	181	-	-	-	3
Mühlendahl et al. [10]	47,XXY	8	-	-	1.1	5	189	15	39	0.1	8
Bertelloni et al. [11]	47,XXY	5	4.2	37	2.8	4	176	16	13	2.9	4
Bertelloni et al. [12]	48,XXYY	7	31	130	4	-	176	45	130	4.2	-
Fryns et al. [13]	47,XXY	-	-	-	-	-	-	-	-	-	-
Gonzales-Ellis et al. [14]	47,XXY	8.5	1.9	-	0.86	-	164	3.5	-	2.7	4
Reported case	47,XXY	8	3.5	24	4.35	6	178	19	22	1.16	4
<b>All (Mean ± SD)</b>		<b>7.5 ± 1.3</b>	<b>9 ± 12</b>	<b>58.2 ± 48</b>	<b>2.7 ± 1</b>	<b>4.6 ± 1</b>	<b>177 ± 7</b>	<b>20 ± 17</b>	<b>51 ± 61</b>	<b>2.2 ± 1.4</b>	<b>4.6 ± 1.7</b>

FSH Follicle stimulating hormone, LH Luteinizing hormone, LHRH Luteinizing hormone-releasing hormone, PP Precocious puberty, T Testosterone levels, TV Testicular volume. Testosterone levels (T) are in ng/ml. TV corresponds to testicular volume in ml. LH and FSH are in UI/l.

with (3 patients including our case) [9, 10] or without anti-androgen treatment (5 patients). This is explained by the potential role of short-stature homeobox gene (SHOX) overexpression in such patients due to their dysgonosomia compensating for an eventual short stature risk related to PP [16]. However, testosterone levels at mid-puberty (14–15 years) and the testicular volume in these ICPP patients are identical to the classical puberty profile of KS [17–20].

Indeed, around 450 boys with ICPP under the age of 9 years have been described in the published cohorts to date, accounting for about 8% of all central precocious puberty cases before the age of 9 year and 10% before the age of 10 years (Supplementary Table 1) [21–33]. The incidence of ICPP in boys is around 0.05/10,000 boys under the age of 9 years and 0.24/10,000 boys under the age of 10 years [32, 34, 35], while the incidence of KS is around 15/10,000 births [36]. Thus, the description of 8 cases of KS in around 450 reported cases of ICPP in the general population suggests an “overrepresentation” of ICPP in Klinefelter patients. The risk is estimated to be 1/370 KS patients by the Health Register of Belgium [13].

The unexpected “overrepresentation” of ICPP in KS raises two hypotheses. Firstly, while gonadotropin levels in KS patients during ICPP are as high as in 15 years old

KS patients without ICPP, the testicular destruction is advanced [17, 37]. Higher gonadotropin levels during ICPP in KS patients compared to those in 46,XY patients suggest that a testicular factor could be a “peripheral initiator of GnRH pulsatility” during precocious puberty that is presumed to be central (ICPP). In KS patients, high estradiol levels is one of the earliest testicular anomalies [38]. Estrogen levels explain the chronological differences in puberty between girls and boys during puberty. Estrogen increases Kiss1 expression (gene coding kisspeptin, a major regulator of GnRH activation) in the hypothalamus during puberty. This effect is exerted through estrogen receptor (Erα). If this process is disrupted, puberty could be delayed [39]. Higher estradiol levels detected early in Klinefelter patients were proposed to precociously activate gonadotropin secretion [28, 31]. Indeed, it has been recently shown that estrogen promotes the expression of genes related to precocious puberty which activate GnRH secretion [40]. Germ cell apoptosis is another early phenomenon in KS [29]. The degree of germ cell apoptosis/seminiferous tissue fibrosis and Leydig cell dysfunction in KS are best reflected by FSH and LH levels respectively. Basal- and stimulated-LH and FSH levels are even higher in the patient with 48,XXYY [12]. This suggests that gonadotropin reserve correlates with the degree of testicular

**Table 3** Gonadotropin levels in patients with ICPP with a normal karyotype (adapted from Pigneur et al. [15]) and ICPP in cases with KS

	LH (UI/l)	LH Post-GnRH (UI/l)	FSH (UI/l)	FSH Post-GnRH (UI/l)	T (ng/ml)
ICPP (Pigneur et al. 2008) (28 patients) (Mean ± SD)[15]	1.1 ± 0.6	15.5 ± 0.8	2.7 ± 1.5	5.7 ± 3.9	2.6 ± 2.1
ICPP+KS (8 cases) (5–9 years) (Mean ± SD)	9.4 ± 12	58 ± 48	23.1 ± 38.5	49.1 ± 62.1	3.1 ± 1.3
Review of cases in the present study					

ICPP Idiopathic central precocious puberty, KS Klinefelter syndrome, FSH Follicle stimulating hormone, LH Luteinizing hormone, GnRH Gonadotropin-releasing hormone, SD Standard deviation, T Testosterone levels. Data are presented as mean ± SD

destruction, which is maximal in 48,XXYY patients. This hypothesis is also supported by the description of ICPP cases in patients with Turner syndrome and cryptorchidism [5, 41, 42]. Indeed, the testicular destruction and/or higher estrogen levels in Klinefelter patients would increase the hypothalamic/pituitary gonadotropin reserve and explain why these patients have higher basal and GnRH-stimulated LH and FSH levels during ICPP. These data are interesting and highlight the timing and role of testicular destruction in dysgonosomia to initiate GnRH pulsatility.

Secondly, in our patient, both X chromosomes were of maternal origin. None of the reported cases studied the origin of the supplementary X chromosome. It is worth noting that the supplementary X chromosome is equally inherited from paternal and maternal origin. When the origin of this supplementary X chromosome is maternal, it is hypothesized that some deleterious genes could escape the natural X chromosome inactivation [43, 44]. These deleterious genes could be responsible for an earlier activation of puberty in such patients [17, 45]. In line with this hypothesis, 2 X-linked gene mutations are described in the literature to be associated with ICPP in 2 boys: *NROB1* (responsible for X-linked adrenal hypoplasia congenita) [46] and *MECP2* (responsible for Rett syndrome) [47]. On the contrary, paternal X chromosome (pX) is associated with further delayed puberty than those with a maternal X chromosome (mX) [17]. Puberty signs with significant increment in LH levels appeared respectively 1.9 and 1.3 years later in patients with pX. Additionally, androgen receptor (AR) gene is located on the X chromosome. It contains CAG repeats in the N terminal domain of exon 1 that could be highly polymorphic. The length of this repetition is inversely correlated with receptor activity [48], and is found to influence clinical presentation of KS [49]. Indeed, shorter CAG repeats and lower AR methylation were linked to premature pubarche [50]. Nevertheless, no study linked CAG repeats or AR activity to precocious puberty in KS patients.

Despite a number of interesting studies investigating early onset of puberty in patients with KS, the genetic basis of idiopathic central precocious puberty in both sexes remains elusive. Further studies using molecular genetics could help understanding the mechanisms of puberty initiation, timing and progression. Specifically, identifying novel X-linked genes in boys with precocious puberty will be instrumental to shed light on the mechanisms underlying puberty initiation.

## Conclusions

ICPP is extremely rare in boys. ICPP patients with KS have higher gonadotropin levels than those with a normal karyotype. This suggests a peripheral or “testicular

driver” that amplifies gonadotropin secretion through a positive feedback loop, which in turn triggers the initiation of central PP in such patients. Furthermore, maternal supplementary X chromosome in KS might play a role in the timing of puberty initiation. In boys with ICPP, long term endocrinological follow up until definitive puberty and karyotype analysis are important, especially if gonadotropin levels are significantly elevated or testicular volume is reduced.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12610-020-00117-1>.

### Additional file 1.

**Additional file 2: Supplementary Table 1.** Incidence of central precocious puberty (ICPP) according to sex. ICPP: Idiopathic central precocious puberty. CPP: Central precocious puberty. ICPP in boys accounts for 10% of the aetiologies of CPP. Data represent number of patients or percentage (%).

### Abbreviations

AR: Androgen receptor; CNV: Copy number variations; CPP: Central precocious puberty; FSH: Follicle stimulating hormone; GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; ICPP: Idiopathic central precocious puberty; KS: Klinefelter syndrome; LH: Luteinizing hormone; LHRH: Luteinizing hormone-releasing hormone; MRI: Magnetic resonance imaging; mX: Maternal X chromosome; PCR: Polymerase chain reaction; PP: Precocious puberty; pX: Paternal X chromosome; SHOX: Short-stature homeobox gene; UI: International units

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### Consent for participation

Patient's written consent is obtained for genetic analyses and participation.

### Authors' contributions

IT, FB, BB, MBL, AL and PT participated in the management of the patient and revised the manuscript, CPR and GS did the cytogenetic studies, KHMK edited the language and revised the manuscript, SM wrote and revised the manuscript. The author(s) read and approved the final manuscript.

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### Availability of data and materials

All the data concerning the case are made available in this manuscript.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Patient's written consent is obtained for publication.

### Competing interests

The authors declare no competing interests.

### Author details

<sup>1</sup>CHU Clermont-Ferrand, Service d'endocrinologie, diabétologie et maladies métaboliques, 58, rue Montalembert, F-63003 Clermont-Ferrand, France.

<sup>2</sup>Université Clermont Auvergne, Faculté de médecine, F-63003

Clermont-Ferrand, France. <sup>3</sup>Laboratoire GRéD, Université Clermont Auvergne, F-63003 Clermont-Ferrand, France. <sup>4</sup>Centre Jean Perrin, Service de Médecine nucléaire, F-63003 Clermont-Ferrand, France. <sup>5</sup>CHU Clermont-Ferrand, service de cytogénétique médicale, F-63003 Clermont-Ferrand, France. <sup>6</sup>Department

of Biosciences and Nutrition, Karolinska Institutet, 141 83 Stockholm, Sweden. <sup>7</sup>CHU Clermont-Ferrand, Service de pédiatrie, F-63003 Clermont-Ferrand, France. <sup>8</sup>Hôpital Pitié-Salpêtrière, service d'endocrinologie et médecine de la reproduction, Centre de maladies endocriniennes rares de la croissance et du développement, Paris, France. <sup>9</sup>Assistance Médicale à la Procréation, CECOS, CHU Clermont-Ferrand, F-63000 Clermont-Ferrand, France. <sup>10</sup>Université Clermont Auvergne, INSERM, U1240 Imagerie Moléculaire et Stratégies Théranostiques, CHU Clermont-Ferrand, F-63000 Clermont Ferrand, France.

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