Treatment of primary infertility in McCune-Albright syndrome: a case report of a successful in vitro fertilization cycle

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Objective: To report a case in which pregnancy and live birth were achieved in an infertile patient with McCune-Albright syndrome via in vitro fertilization (IVF).
Design: Case report.
Setting: University hospital.
Patient(s): A 29-year-old woman with McCune-Albright syndrome who presented with primary infertility due to ovulatory dysfunction and bilateral tubal blockage.
Intervention(s): In vitro fertilization without unilateral oophorectomy.
Main Outcome Measure(s): Live birth after IVF treatment.
Result(s): Fresh IVF stimulation and bilateral oocyte retrieval yielded 12 oocytes and 4 top quality embryos. Fresh single embryo transfer did not result in pregnancy. Live birth occurred after the second frozen embryo transfer cycle.
Conclusion(s): In vitro fertilization can lead to ongoing pregnancy in infertile patients with McCune-Albright syndrome without requiring unilateral oophorectomy. (Fertil Steril Rep® 2021;2:352–6. ©2021 by American Society for Reproductive Medicine.)
Key Words: McCune-Albright syndrome, infertility, in vitro fertilization

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INTRODUCTION

Precocious puberty, polyostotic fibrous dysplasia, and café au lait spots are the classic triad of symptoms that characterize McCune-Albright syndrome (MAS). These manifestations are caused by a sporadic, activating mutation of the G protein alpha subunit that results from a missense point mutation at codon 201 of the GNAS1 gene in which arginine is replaced with histidine or cysteine (1–4). This mutation is detected in some but not all tissues. The distribution of affected tissues is predominantly unilateral, and the mosaic nature of this disorder arises from a somatic mutation occurring during embryogenesis (3, 4). The effects of this mutation in the ovary cause unregulated peripheral estrogen production that is independent of the levels of gonadotropins. Thus, women with MAS not only have the classic triad of childhood symptoms as described previously, but also develop other gynecologic disorders during adulthood such as abnormal uterine bleeding, ovarian cysts, and ovulatory dysfunction (5, 6).

Since MAS was first described in 1936 (7, 8), studies have mainly focused on the treatment of precocious puberty in children. Currently, there is limited understanding on how MAS affects fertility and, therefore, how infertility should be treated in adult patients with MAS. Infertility is significantly increased in women with MAS with a prevalence of 43% based on a recent study (5), but only four case reports on the management of infertility have been published. All of these case reports establish that the removal of the affected ovary is an effective option to restore ovarian function and treat infertility (9–12). Here, we report the first case of in vitro fertilization (IVF) stimulation in a woman with ovarian dysfunction due to MAS.

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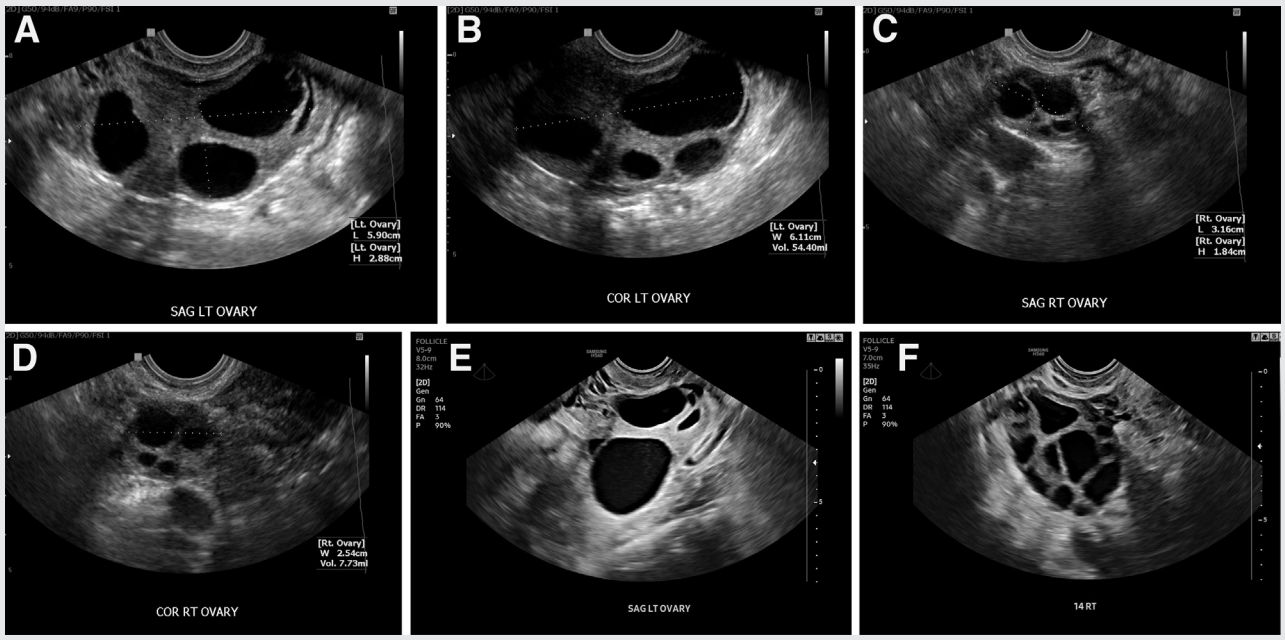
FIGURE 1



Transvaginal ultrasound images of baseline left ovary measuring 6.1 × 5.9 × 2.9 cm, with a volume of 54.4 mL in the (A) sagittal and (B) coronal views. Baseline right ovary measuring 3.2 × 2.5 × 1.8 cm, with a volume of 7.7 mL in the (C) sagittal and (D) coronal views. (E) Left ovary at trigger. (F) Right ovary at trigger.

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CASE REPORT

The patient provided consent before submission of this case report. A 29-year-old nulliparous woman presented with primary infertility of 2-year duration and irregular menstrual periods. She had a known history of MAS diagnosed at the age of 2 years. Her clinical manifestations included precocious puberty and menarche at the age of 10 years; fibrous dysplasia of her left leg, facial bones, and left skull; and a history of femur fractures with rod placement. The patient was diagnosed at the NIH in Bethesda, Maryland, and was observed up until 2018; recent medical records did not indicate whether genetic testing was performed to confirm her diagnosis. The patient had a past medical history of vitamin D deficiency and type 2 diabetes mellitus, which was managed with metformin and insulin. The patient had a body mass index of 32 and a blood pressure of 130/80 mm Hg.

When the patient presented for evaluation, previously obtained random laboratory tests showed levels of estradiol (E2), 273 pg/mL; follicle-stimulating hormone (FSH), 0.2 mIU/mL; luteinizing hormone (LH), 0.1 mIU/mL; thyroid-stimulating hormone, 1.47 mIU/mL; hemoglobin A1c (HgbA1c), 7.3%; growth hormone, 1.06 ng/mL; prolactin, 5.9 ng/mL; insulin-like growth factor, 121 ng/mL; and antimüllerian hormone, 2.5 ng/mL. Cycle day 3 baseline laboratory tests were also performed, which revealed the following results: E2, 205 pg/mL; FSH, 0.5 mIU/mL; and LH <1.0 mIU/mL. As the patient had a history of type 2 diabetes, she worked closely with her primary care provider to improve her glycemic control and to decrease her HgbA1c level to 6.1% before the start of IVF stimulation. The threshold for HgbA1c at our institution was 6.5%.

Semen analysis showed normal results. Ultrasound revealed an asymmetrically enlarged left ovary measuring 6.1 × 5.9 × 2.9 cm, with a volume of 54.4 mL. The left ovary also had 25 follicles, 7 of those measured >10 mm (Figure 1). The right ovary was otherwise unremarkable and measured 3.2 × 2.5 × 1.8 cm with a volume of 7.7 mL. Hysterosalpingogram (HSG) showed bilateral tubal occlusion but no hydrosalpinges. The patient was advised to undergo laparoscopic chromopertubation, or repeat HSG, but given the presence of bilateral tubal blockage, the patient opted to proceed with IVF. She was counseled regarding the possible risks of IVF stimulation, such as the unknown aspects of stimulation, the risk of ovarian torsion and ovarian hyperstimulation, and difficulty in monitoring her E2 levels and follicular sizes.

Due to concerns regarding prolonged pituitary suppression from persistently elevated E2 levels, letrozole (5 mg daily) was administered for 30 days. A repeat laboratory test was performed at the end of 30 days and showed the following results: a decrease in E2 level to 61 pg/mL, an FSH level of 6.9 mIU/mL, an LH level of 4.8 mIU/mL, and a progesterone (P4) level of 0.60 ng/ml, indicating a quick reversal of pituitary suppression. A repeat ultrasound revealed a decrease in the size and number of left ovarian cysts, as well as a trilaminar endometrial lining measurement of 6.4 mm. Withdrawal bleeding was induced with a 10-day course of medroxyprogesterone in combination with letrozole. During the patient's menstrual period, a baseline

TABLE 1

In vitro fertilization stimulation.

Cycle day	HMG (IU)	Ganirelix (mcg)	Estradiol (pg/mL)	Progesterone (ng/mL)	Endo (mm)	Right ovary Lead follicles (mm) Follicles > 10 mm/total no.	Left ovary Lead follicles (mm) Follicles > 10 mm/total no.
Baseline			39	0.3	4.7	None 0/7	None 0/20+
1–3	225						
4	300		114				
5	300						
6	300		170	0.9	3.9	None 0/8	24, 11 2/20+
7	375	250					
8	375	250					
9	375	250	188	0.5	6.4	None 0/12	27, 12 2/20+
10	375	250					
11	375	250	364	0.5	6.9	14, 12, 12 3/12	26, 13, 12, 11 4/20+
12	375	250					
13	375	250	884	0.5	8.4	17, 16, 16, 15, 13, 11 6/13	26, 18, 15, 11 4/20+
14	375	250					
15		250	1,040	0.5	10.7	22, 21, 21, 16, 14, 13, 12 7/14	29, 19, 17, 12 4/20+

HMG = Human menopausal gonadotropin.

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scan before the start of the cycle was performed which unfortunately showed interval development of a 3.5-cm cyst on the right ovary. Letrozole was discontinued, and an oral contraceptive pill was administered for 3 weeks until the eventual resolution of the cyst.

An antagonist protocol was started with a plan to schedule the trigger injection based on the follicle sizes of the right, unaffected ovary. At baseline, the left, affected ovary had three follicles measuring >10 mm (13–17 mm). However, a repeated laboratory test was performed which showed an E2 level of 39 pg/mL, a P4 level of 0.30 ng/mL, an FSH of 0.3 mIU/mL, and an LH level of <1.0 mIU/mL. Human menopausal gonadotropin (Menopur 225 IU) was initiated, which was increased to 300 IU on cycle day 4. On cycle day 6, her left ovary showed a 24-mm follicle. Gonadotropin-releasing hormone (GnRH) antagonist (Ganirelix) was started on cycle day 7, while human menopausal gonadotropin was increased to 375 IU. On day 11, the right ovary had started to recruit a cohort of follicles. She was triggered with human chorionic gonadotropin (hCG) on cycle day 15 with 7 follicles measuring >10 mm (12–22 mm) on the right ovary and 4 follicles measuring >10 mm (12–29 mm) on the left ovary. Her endometrial lining measured 10.7 mm, and the E2 level increased to 1,040 pg/mL. Table 1 shows the details regarding the patient's stimulation cycle. During the period of ovarian stimulation, subsequent ultrasounds showed a 4-cm left hydrosalpinx.

At the time of the retrieval, the embryologist noted MII oocytes from both the right and left ovary. A total of 12 oocytes were retrieved, 9 of which were mature and were inseminated by intracytoplasmic sperm injection. Of the 9 oocytes, 4 were fertilized normally. A fresh single embryo transfer (ET) of a hatching AA blastocyst was performed on day 5, and three blastocysts were cryopreserved. Intramuscular P4 was administered on the day of retrieval for luteal support. The results of laboratory tests performed 11 days posttransfer were as follows: hCG, <2 mIU/mL; E2, 23 pg/mL; and P4, 18 ng/mL; the patient was unable to conceive.

Due to an unsuccessful fresh ET, a recommendation for further investigation of her left hydrosalpinx with a repeat HSG versus laparoscopy was discussed with the patient. The patient opted to proceed with laparoscopy and chromopertubation. Findings showed the absence of spill bilaterally and a left hydrosalpinx; therefore, a left salpingectomy was performed, and the ovaries remained in situ.

The patient underwent a frozen embryo transfer (FET) using our standard endometrial preparation of oral E2 (2 mg three times daily) for 14–21 days and intramuscular P4 in oil 50 mg 5 days before ET. In cycle 2, a single ET of an expanded AA blastocyst was performed resulting in a biochemical pregnancy. In cycle 3, a FET of her remaining two embryos graded as hatching AA blastocyst and expanded BA blastocyst was performed. An early ultrasound showed twin pregnancy with the demise of one twin and a viable intrauterine gestation of the other twin; the patient was then released to obstetric care. Gestational hypertension was induced, and the patient had a term vaginal delivery of a male infant weighing 7 lbs 11.5 ounces. Genetic analysis of the placenta was not performed.

DISCUSSION

McCune-Albright syndrome was first recognized in 1936 by McCune and then by Albright in 1937 (7, 8); however, the first

publication that described the treatment of the symptoms of MAS was not published until 1951, which noted the arrest and even the regression of secondary sexual characteristics after the surgical resection of the enlarged cystic ovary (13). Since then, the literature focuses mainly on the treatment of precocious puberty in children with MAS. In adulthood, other gynecologic issues such as infertility play a larger role, but there is limited understanding regarding the management of infertility in MAS patients despite the high prevalence of infertility in this population (5).

Four other case reports have been conducted to evaluate the management of infertility in MAS, all of which demonstrated that unilateral oophorectomy resulted in the return of ovulatory function and pregnancy. Two patients had an unsuccessful ovulation induction or controlled ovarian stimulation before surgical management; these details were not described in-depth (11–12). After performing surgical management, all four patients got pregnant with spontaneous conception or subsequent IVF, except for one patient who was not yet ready for pregnancy after surgery (9–12). In this case report, the option for surgical management was not desirable because the resumption of spontaneous menses would not improve the fertility outcome of this MAS patient due to tubal factor infertility which could compromise the ovarian reserve. Therefore, an alternative treatment to surgery had to be considered. This is the first known case report to discuss the treatment of infertility in a MAS patient with two novel concepts: without unilateral oophorectomy; and with IVF.

The benefits of foregoing surgical management as the primary treatment option include protecting the ovarian reserve and decreasing the risks associated with surgery.

Although MAS tends to be unilaterally involved, the bilateral involvement of the ovaries has been documented (10). Due to the fluctuations in ovarian size, it may not always be obvious which ovary is involved without performing genetic testing of the tissue (14–16). This patient did not undergo ovarian tissue genetic analysis. Thus, surgery risks the possibility of removing the unaffected ovary, compromising the ovarian reserve, and finding that ovarian function did not improve postoperatively.

The other considerations include costs and time to pregnancy. With surgical management, regular ovulatory cycles have been reported to return immediately and two cases resulted in spontaneous pregnancy at three months (9–12). Surgical management may result in spontaneous pregnancy and help the patient build a family without the cost and time associated with IVF to achieve pregnancy. At the time of surgery (left salpingectomy), we explored the possibility of removal of the affected ovary. However, our patient not only had infertility due to anovulation but also bilateral tubal occlusion. Again, surgical management with the return of normal menses was unlikely to improve the chances of spontaneous pregnancy in the future.

Second, this case report emphasized that IVF can be safe and successful in MAS patients without surgery. Although this is the first report of its kind, a recent case series described the successful IVF and pregnancies in patients with FSH-secreting adenomas who did not undergo pituitary surgery, suggesting that IVF in a similar patient population is feasible and that surgery is not always required (17).

Some considerations for the IVF stimulation include the management of an elevated E2 to mitigate the risk of ovarian hyperstimulation syndrome (OHSS), the occurrence of ovarian torsion, and the optimization of ovarian response. Although we do not understand the risk of OHSS in MAS patients, there is a theoretical elevated risk due to high E2 levels based on the data surrounding patients with polycystic ovary syndrome (18–21) as well as reports of spontaneous OHSS in patients with gonadotroph adenomas (22–23). Previous studies have shown that MAS patients are responsive to aromatase inhibitors. Letrozole treatment in young MAS patients with precocious puberty is effective in reducing the rate of bleeding, bone age advancement, and growth velocity (24–25). We opted to reduce the baseline E2 with letrozole for 30 days before IVF stimulation. This allowed the use of E2 as a surrogate marker of follicular development as well as the reduction of the peak E2 at the time of trigger. The quick reversal of pituitary suppression provided reassurance that we could proceed with a leuprolide trigger if needed. We chose an antagonist protocol again to give the option for a leuprolide trigger and a freeze-all cycle if concerns for OHSS developed. At the time of trigger, standard hCG dosing of 10,000 IU was used as the patient was at low risk for OHSS. Close monitoring of E2 levels and follicular growth during stimulation as well as postretrieval symptoms is essential until the risk for OHSS has been established in MAS patients. Although the elevated serum E2 levels do not appear to affect the oocyte or embryo quality (26), the supraphysiologic levels can negatively affect the endometrial receptivity in the fresh cycle (27).

With both ovaries in situ, we were able to retrieve mature oocytes from the affected left ovary, demonstrating that the affected ovary does not influence the ovarian reserve. In MAS patients, rapid follicular growth and premature luteinization have been previously described (6). In this report, the left ovary at baseline had multiple >10-mm follicles despite a low E2 level. It quickly produced a dominant follicle likely due to its autonomous stimulation of follicles rather than the response to exogenous gonadotropin. Because of the development of a large follicle, GnRH antagonist treatment was initiated to reduce the risk of premature luteinization. With GnRH antagonist on-board, we were able to use the response of the right unaffected ovary to determine the appropriate time for triggering final maturation.

Unfortunately, after retrieval, the specific ovary in which each oocyte originated was not traced during fertilization and embryo culture. We recognize this as a limitation of this case report. For future studies, evaluating the fertilization and blastulation rates of oocytes retrieved from each ovary would provide insight into whether the affected ovary contributes to successful fertilization and top quality embryo development.

Lastly, after the fresh ET, our patient's E2 level was notably low. This could be due to pregnancy failure. Alternatively, the corpora lutea on the affected ovary may be dysfunctional in MAS patients. Based on follicular fluid studies, MAS patients can have a normal corpus luteum function on the unaffected ovary (6) compared with that on an

affected ovary. In IVF with multiple corpora lutea formation on both ovaries, any dysfunction can be overcome. Intramuscular P4 supplementation was the only management used for luteal support during the FET, but future studies may consider the use of both estrogen and P4.

Treating infertility in women with MAS is an area of reproductive medicine that has been largely undescribed. To date, surgical management with unilateral oophorectomy has been the only published option to achieve a successful pregnancy. This case report expands our understanding of infertility treatment in women with MAS and demonstrates that IVF with bilateral ovaries left in situ is a viable option for these women.

REFERENCES

1. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991;325:1688–95.
2. Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. J Pediatr 1993;123:509–18.
3. Lumbroso S, Paris F, Sultan C. McCune-Albright syndrome: molecular genetics. J Pediatr Endocrinol Metab 2002;15:875–82.
4. Happle R. The McCune-Albright syndrome: a lethal gene surviving by mosaicism. Clin Genet 1986;29:321–4.
5. Boyce AM, Casey RK, Ovejero Crespo D, Murdock CM, Estrada A, Guthrie LC, et al. Gynecologic and reproductive outcomes in fibrous dysplasia/McCune-Albright syndrome. Orphanet J Rare Dis 2019;14:90.
6. Laven JS, Lumbroso S, Sultan C, Fauser BC. Dynamics of ovarian function in an adult woman with McCune-Albright syndrome. J Clin Endocrinol Metab 2001;86:2625–30.
7. McCune DJ. Osteitis fibrosa cystica: the case of a nine-year-old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. Am J Dis Child 1936;52:743–4.
8. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. N Engl J Med 1937;216:727–46.
9. Laven JS, Lumbroso S, Sultan C, Fauser BC. Management of infertility in a patient presenting with ovarian dysfunction and McCune-Albright syndrome. J Clin Endocrinol Metab 2004;89:1076–8.
10. Lavoué V, Morcel K, Bouchard P, Sultan C, Massart C, Grall JY, et al. Restoration of ovulation after unilateral ovariectomy in a woman with McCune-Albright syndrome: a case report. Eur J Endocrinol 2008;158:131–4.
11. Chevalier N, Paris F, Fontana S, Delotte J, Gaspari L, Ferrari P, et al. Postpubertal persistent hyperestrogenemia in McCune-Albright syndrome: unilateral oophorectomy improved fertility but detected an unexpected borderline epithelial ovarian tumor. J Pediatr Adolesc Gynecol 2015;28:e169–72.
12. Chanson P, Salenave S, Young J. Ovarian dysfunction by activating mutation of GS alpha: McCune-Albright syndrome as a model. Ann Endocrinol (Paris) 2010;71:210–3.
13. Pray LG. Sexual precocity in females; report of two cases, with arrest of precocity in the McCune-Albright syndrome after removal of a cystic ovary. Pediatric 1951;8:684–92.
14. Foster CM, Feuillan P, Padmanabhan V, Pescovitz OH, Beitins IZ, Comite F, et al. Ovarian function in girls with McCune-Albright syndrome. Pediatr Res 1986;20:859–63.
15. Kaufman FR, Costin G, Reid BS. Autonomous ovarian hyperfunction followed by gonadotrophin-dependent puberty in McCune-Albright syndrome. Clin Endocrinol (Oxf) 1986;24:239–42.
16. Pasquino AM, Tebaldi L, Cives C, Maciocci M, Boscherini B. Precocious puberty in the McCune-Albright syndrome. Progression from gonadotrophin-independent to gonadotrophin-dependent puberty in a girl. Acta Paediatr Scand 1987;76:841–3.
17. Ren Y, Wang JJ, Wang LN, Wang Y, Qiao J, Zhen XM, et al. Management of infertility and long-term follow-up in women with follicle-stimulating hormone-secreting adenoma. Chin Med J (Engl) 2021;134:101–3.
18. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017;23:560–79.
19. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, et al. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). Hum Reprod 2010;25:683–9.
20. Cardone VS. GnRH antagonists for treatment of polycystic ovarian syndrome. Fertil Steril 2003;80:25–31.
21. Ragni G, Vegetti W, Riccaboni A, Engl B, Brigante C, Crosignani PG. Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome. Hum Reprod 2005;20:2421–5.
22. Baba T, Endo T, Kitajima Y, Kamiya H, Moriwaka O, Saito T. Spontaneous ovarian hyperstimulation syndrome and pituitary adenoma: incidental pregnancy triggers a catastrophic event. Fertil Steril 2009;92:390.e1–3.
23. Caretto A, Lanzi R, Piani C, Molgora M, Mortini P, Losa M. Ovarian hyperstimulation syndrome due to follicle-stimulating hormone-secreting pituitary adenomas. Pituitary 2017;20:553–60.
24. Feuillan P, Calis K, Hill S, Shawker T, Robey PG, Collins MT. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. J Clin Endocrinol Metab 2007;92:2100–6.
25. Estrada A, Boyce AM, Brillante BA, Guthrie LC, Gafni RI, Collins MT. Long-term outcomes of letrozole treatment for precocious puberty in girls with McCune-Albright syndrome. Eur J Endocrinol 2016;175:477–83.
26. Peña JE, Chang PL, Chan LK, Zeitoun K, Thornton MH, Sauer MV. Supraphysiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. Hum Reprod 2002;17:83–7.
27. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. Fertil Steril 2011;96:516–8.