First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids

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Objective: To study the pregnancy rate after ulipristal acetate (UPA) therapy for fibroids.
Design: Retrospective analysis of a series of 52 patients prospectively included in the PGL4001 (ulipristal acetate) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL) II and III trials.
Setting: Academic hospital.
Patient(s): Among the 52 patients, 21 wished to conceive upon treatment completion.
Intervention(s): None.
Main Outcome Measure(s): Pregnancy rate and live birth rate.
Result(s): Twenty-one patients attempted to get pregnant, among whom 15 (71%) succeeded, totaling 18 pregnancies. Among these 18 pregnancies, 12 resulted in the birth of 13 healthy babies and 6 ended in early miscarriage. No regrowth of fibroids was observed during pregnancy.
Conclusion(s): We report the first series of pregnancies achieved after UPA treatment. Our data confirm a sustained long-term effect after UPA therapy. (Fertil Steril® 2014;102:1404–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Fibroids, selective progesterone receptor modulators (SPRMs), ulipristal acetate, pregnancy

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Ulipristal acetate (UPA), a selective P receptor modulator (SPRM) with pharmacokinetic properties allowing a single daily dose, potently modulates P activity and exerts proapoptotic antiproliferative effects on fibroid cells without suppressing E_2 to nonphysiologic levels. Two randomized clinical trials have shown that UPA is efficient for control of excessive bleeding in patients with symptomatic uterine fibroids (1, 2). It also reduces myoma size and uterine volume, found to be maintained for at least 6 months in patients not undergoing surgery (1, 2). Rapid control of bleeding serves to normalize hemoglobin levels, which is important before a surgical procedure, because we know that anemia, even to a mild degree, increases the risk of postoperative morbidity and mortality in both cardiac and noncardiac surgery (3).

Administration of SPRMs induces endometrial changes (P receptor modulator–associated endometrial changes, PAECs), which spontaneously reverse over a period of several weeks to months after cessation of UPA therapy (4). Very recently a strategy involving intermittent courses of 12-week UPA treatment with off-treatment intervals was demonstrated to be a potential option for long-term medical management of fibroids (5). New algorithms were proposed to evaluate the remaining place of myoma surgery in current practice (6).

To date, no data on fertility or pregnancy after UPA are available from the literature.

Here we report the first series of 18 pregnancies obtained in 15 infertile patients who underwent UPA therapy.

MATERIALS AND METHODS

The PGL4001 (ulipristal acetate) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL) II and III trials were approved by our local ethics committee and were conducted in accordance with the International Conference on Harmonization–Good Clinical Practice guidelines.

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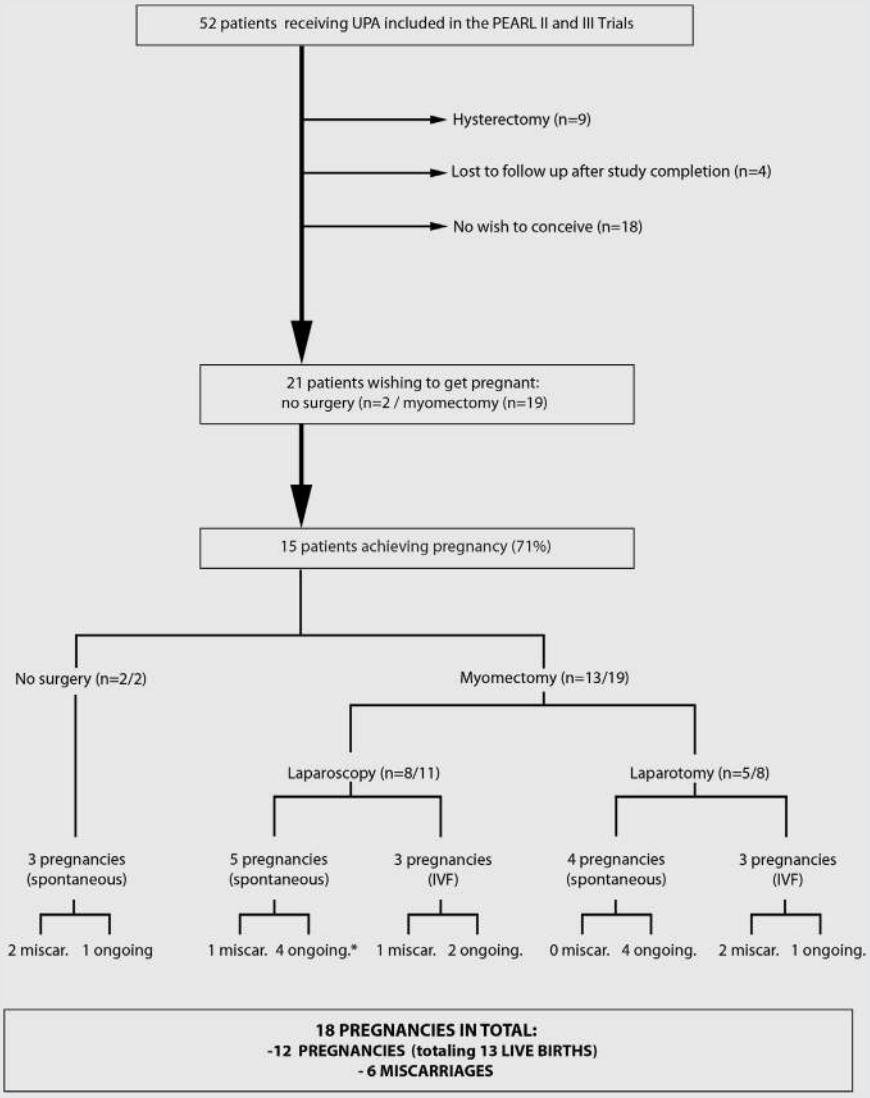
Fifty-two patients with symptomatic fibroids were prospectively included in the PEARL II and PEARL III trials at our institution, according to strict inclusion criteria (2, 5), and received UPA treatment (Fig. 1). This report is a retrospective analysis of pregnancies and births achieved in this series of 52 patients. Ten women were given 5 mg UPA for 3 months (PEARL II) (2), and 42 women received 10 mg UPA for variable periods of time (3 months [n = 27], 6 months [n = 2], 9 months [n = 7], 12 months [n = 6]) according to the PEARL III protocol (5). Among these 52 patients, 21 wished to conceive upon treatment completion and were followed accordingly. Figure 1 shows the distribution of patients.

Of these 21 patients, 19 (90.5%) underwent myomectomy at the end of therapy, according to the protocol.

Two patients did not require surgery because of an almost complete disappearance of their fibroids. The first patient presented with menorrhagia due to uterine myomatosis. She had no wish to conceive at that time. Uterine volume was equivalent to 10 weeks of pregnancy (Fig. 2A) at the first consultation. (The uterine size was evaluated in weeks of gestation to conform to the protocol accepted by US Food and Drug Administration and European Union regulatory authorities and could not be modified to uterine volume in cm^3 retrospectively.) She was given UPA therapy over four courses of 3 months, according to the PEARL III protocol (5). At the end of treatment only tiny myomas remained, and vaginal examination and magnetic resonance imaging (MRI) showed a uterus of normal volume (Fig. 2B). At her checkup 3 months after treatment completion, the fibroids were stable in size. In line with the extension protocol (bis) of the PEARL III study, it was proposed that the patient start another course of UPA treatment, because she had no clear desire for pregnancy. On the first day of menstruation she began taking 10 mg UPA (retrospectively, the bleeding that the patient interpreted as menstrual bleeding

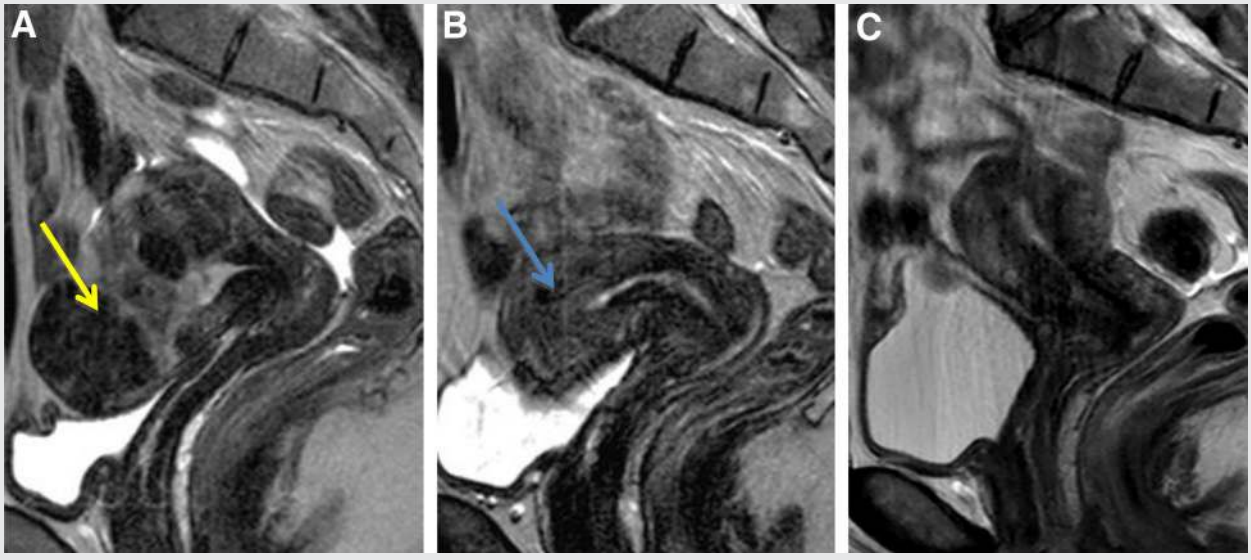
FIGURE 1



Distribution of pregnant patients included in the study. *One patient had twins. UPA = ulipristal acetate; IVF = in vitro fertilization; miscar = miscarriage.

Luyckx. Pregnancies after ulipristal acetate. Fertil Steril 2014.

FIGURE 2



(**A**) Initial MRI. (**B**) End of treatment. (**C**) After delivery. Complete response after four courses of 3-month therapy with 10 mg of UPA, and no regrowth during pregnancy or after delivery. The largest anterior myoma, measuring approximately 4 cm (*blue arrow*), disappeared completely at end of treatment. Only small intramyometrial fibroids, less than 1 cm (*yellow arrow*) remained, with no consequence on the uterine cavity. A few months later the patient achieved a spontaneous pregnancy, with no larger fibroids detected in the course of the pregnancy. Control MRI was performed 10 months after delivery and did not show any myoma regrowth.

Luyckx. Pregnancies after ulipristal acetate. Fertil Steril 2014.

was in fact periovulatory bleeding). She continued the therapy for 36 days. Early pregnancy was diagnosed at her first checkup, and she immediately stopped the medication.

The second patient, aged 40 years, presented with menorrhagia and a fibroid of 3 cm distorting the uterine cavity (International Federation of Gynecology and Obstetrics class 2) (7). She already had two children but was hoping to conceive again. Her submucous fibroid was found to have disappeared by the end of treatment, and no surgery was required.

RESULTS

Among the 21 patients wishing to conceive (Fig. 1), 19 were operated on after UPA therapy: 11 by laparoscopy and 8 by laparotomy. Two patients did not undergo surgery. Fifteen women (71%) became pregnant, resulting in 18 pregnancies. Of these, 12 resulted in the delivery of 13 healthy babies, and 6 ended in early miscarriage (one patient experienced two miscarriages) (Fig. 1).

Six patients (29%) did not manage to conceive. In these women, associated factors were found: age over 40 years in three, concomitant adenomyosis in one, and age over 38 years in two.

Characteristics of the 15 pregnant patients are detailed in Table 1. Mean age was 36.4 years (range, 23–44 years), with only one patient aged <30 years. Nine patients were nulliparous, and four had already experienced miscarriage. One patient had previously undergone myomectomy by laparotomy. Two patients had had other gynecologic surgery: one salpingectomy and one cystectomy for endometriosis. Mean uterine volume upon screening was equivalent to 10.8 weeks of pregnancy (range, 7–16 weeks). The number of myomas removed at surgery was greater than five in 66% of patients (10 of 15).

Thirteen patients attempted to conceive from 3 months after finishing their therapy and got pregnant between 3 and 14 months after treatment completion or surgery (median, 10 months). Two patients did not attempt to get pregnant immediately but were looking to conceive in approximately a year. They became pregnant after, respectively, 8 and 10 months of trying (unprotected sexual intercourse).

In total, 18 pregnancies were obtained in this group of 15 women. Among these 18 pregnancies, 12 were ongoing and 13 healthy babies were delivered (one patient had twins) (Fig. 1). Among the 11 patients who delivered, one had twins and another had two healthy babies (Fig. 1).

During pregnancy, one patient experienced cervical incompetence treated by cerclage, with good evolution and delivery at 38 weeks.

The fetus of the mother who took UPA for 36 days at the beginning of pregnancy was diagnosed in utero with an ectopic right kidney. No complications were noted during pregnancy, and the baby was delivered by cesarean section for fetal concerns during labor. The baby's renal function was normal. She was followed by a pediatrician and required no further treatment.

Three patients who experienced pre-eclampsia (PE) were of African ethnicity, respectively 35, 38, and 36 years of age. Two had pre-existing hypertension, and the third developed hypertension early in the pregnancy. The delivery term in PE patients was respectively 29 weeks, 36 weeks plus 5 days, and 36 weeks (twin pregnancy). They all gave birth by

TABLE 1

Characteristics of patients pregnant after UPA treatment and details of the 12 ongoing pregnancies.

Characteristic	No. of patients (N = 15)
Age, y	
<30	1
30–35	4
35–40	6
>40	4
Mean (range)	36.4 (23–44)
Uterine volume (wk of amenorrhea)	
<8	2
8–10	4
10–12	3
>12	6
Mean (range)	11 (7–16)
Nulliparity	9
Previous myomectomy	1
No. of fibroids (MRI evaluation)	
1	3
1–5	2
>5	10
Surgery	13
Laparoscopy	8
Laparotomy	5
Hysteroscopy	2[a]
Pregnancy	18
Spontaneous	12
IVF	6[b]
Patients giving birth	12[c]
Mean term, wk ± d (range)	37 ± 4 (29–40 ± 6)
Complications	5
Cervical incompetence	1
Pre-eclampsia	3
Atrial fibrillation	1
Delivery	
Cesarean section	11
Elective	7
Emergency	4
Vaginal delivery	1
Postpartum complications	0
Premature delivery	3
Neonatal complications	0
Fetal malformations	1 (ectopic right kidney)

[a] Two patients had a hysteroscopy associated with laparoscopic myomectomy.
[b] Two patients obtained pregnancy by oocyte donation because of age.
[c] One patient had twins, resulting for in 13 healthy babies for the whole cohort.

Luyckx. Pregnancies after ulipristal acetate. Fertil Steril 2014.

cesarean section, and the infants received neonatal care. The first patient was the youngest but presented with the most severe PE. She was treated for hypertension in the postpartum period. Two years after the first birth she managed to go until 38 weeks in a second pregnancy, with no PE recurrence.

The mean delivery term was 37 weeks ± 4 days (range, 29–40 weeks ± 6 days). One patient had a vaginal delivery, seven patients an elective, planned cesarean section, and four an emergency cesarean section (three for PE, one for a fetal condition).

Neonates of adequate maturity stayed with their mothers with no complications.

There was no regrowth of fibroids during pregnancy, even in women who did not undergo surgery after the end of treatment.

No postpartum complications were noted, either early- or late-onset complications. No recurrence of symptomatic fibroids has been observed so far in a follow-up ranging from 2.5 to 6 years. One patient, now aged 40 years, underwent laparoscopic myomectomy in 2008 and gave birth in 2010 after undergoing UPA therapy (5 mg, 3 months). Six years later she experienced a recurrence of heavy menstrual bleeding due to severe adenomyosis, necessitating a hysterectomy in 2014.

DISCUSSION

Here we describe the first series of pregnancies achieved after UPA treatment for uterine fibroids. In this series, two patients conceived after taking UPA without the need for surgery, thanks to an excellent response to the treatment.

Twenty-one patients attempted to get pregnant, among whom 15 (71%) succeeded, totaling 18 pregnancies. Among these 18 pregnancies, 12 resulted in the birth of 13 healthy babies, and 6 ended in early miscarriage (6 of 18, 33%). We should stress that all pregnancies, including those that ending in miscarriage, occurred from 3 months after the end of treatment and surgery. The miscarriage rate may well be related to the age of the population. Indeed, the median age of these patients was 38 years. The woman who experienced two miscarriages was more than 40 years old, and it is widely known that age is a major factor in infertility and increases miscarriage rates (8). Moreover, among the six miscarriages, three occurred after IVF, also known to have a higher miscarriage rate than natural conception (9).

Six pregnancies were obtained by IVF, in most cases performed because of age, but also in women with numerous fibroids before surgery, and therefore at higher risk of recurrence, to ensure swift conception (10).

The mean interval to achieve pregnancy after the end of the treatment was 10 months for patients starting directly upon treatment completion or after surgery. Patients who underwent surgery before trying to conceive were asked to wait 3 months to avoid too early a pregnancy on a cicatricial uterus. However, there is no consensus in the literature concerning the optimal interval (10–12). There is no evidence that laparoscopy differs from laparotomy in terms of risk of rupture, and not enough articles to assess their impact on pregnancy rates (13, 14).

In our study there was no significant fibroid regrowth during pregnancy (Fig. 2C). It is widely known that fibroid regrowth during pregnancy is due to high P concentrations, with high levels of P receptors observed in myomas believed to be responsible (10, 15, 16). It is also well established that estrogen has an important effect on fibroid growth. The actions of both estrogen and P are mediated by growth factors, cytokines, and chemokines (reviewed in reference 17). Apoptosis and the sustained decrease in myoma size seen after UPA treatment could explain the absence of regrowth during pregnancy, despite high levels of circulating P (1, 2, 5).

Eleven cesarean sections were performed among the 12 deliveries in this series; 7 were elective cesarean sections. The presence of multiple deep myometrial incisions was the indication for cesarean section in these cases. Recommendations to allow vaginal delivery after myomectomy are

unclear, and even if the risk of uterine rupture is low, its consequences can be disastrous (12–14). We recommend cesarean section in case of multiple deep incisions or large fibroids, as assessed by the surgeon (10–12, 14), and certainly in case of anticipated difficult and long labor.

In four cases emergency cesarean section was carried out: one for a fetal condition and three due to PE.

We encountered three premature births due to PE. Pre-eclampsia is a rare and severe disorder, causing maternal mortality and morbidity, preterm birth, fetal death, and intrauterine growth restriction, and its prevalence varies between 2% and 7 % in healthy nulliparous women (18). The main risk factors are multiparity, chronic hypertension, previous PE, pregestational diabetes mellitus, and pre-existing thombophilia (19). Two patients who developed PE in our series had previous hypertension as a major risk factor, and two also had diabetes. All three were aged >35 years and of African origin. Ulipristal acetate intake was not related to the prevalence of PE, because hypertension was present before UPA treatment. Moreover, one woman had a successful second pregnancy and reached 38 weeks with no PE problems, taking appropriate antihypertensive drugs (18, 19).

We only observed one fetal anomaly, as already mentioned, in a patient who started a new course of treatment when she was already (unexpectedly) pregnant. The fetus showed an ectopic right kidney on the inferior pole of the left kidney. Renal agenesis and ectopic kidneys are considered as congenital malformations, isolated or associated with other malformations or chromosomal or nonchromosomal syndromes (20). Hormone intake by the mother has not been described to have an influence on renal morphogenesis, which seems to be a self-regulating process involving complex molecular mechanisms and gene regulation during fetal life (21, 22). In addition, a review of pregnancies after exposure to mifepristone (given to induce abortion) or UPA (given for emergency contraception), respectively, shows no additional risk of congenital anomalies (23, 24). The baby showed no renal function anomaly and no signs of vesicoureteral reflux. The neonatology team concluded that UPA treatment played no role in this renal anomaly.

Selective progesterone receptor modulators are also known to induce endometrial modifications, namely PAECs, especially when given for a long period of time (4, 25). Studies analyzing PAEC during and after treatment with UPA show that signs of PAEC are frequent (60%) at the end of 3 months' therapy, but this effect is reversible after a few months, even in case of long-term intermittent use (1, 2, 4, 5). Pregnancies obtained in this series demonstrate that these modifications are totally reversible and that endometrium is of sufficient quality for blastocyst implantation, because patients treated with UPA were able to conceive quickly and easily, even those with other infertility factors.

In the long-term follow-up of these patients, only one suffered a recurrence of menorrhagia due to severe adenomyosis and underwent a hysterectomy in 2014, 4 years after the birth of her child. The other 14 patients have stable disease, and none of them have required further medical treatment or surgery for symptomatic fibroids, including those who did not undergo myoma surgery. The recurrence rate is thus much lower than the recurrence rate after myomectomy, which is calculated to be 40% at 4 years according to a recent review (6). These data are in accordance with the findings of the PEARL I, II, and III trials, showing a sustained long-term effect after UPA treatment (1, 2, 5).

In conclusion, here we report the first series of pregnancies achieved after UPA treatment, with a pregnancy rate of 71% in the group of patients wishing to conceive. We also describe, for the first time, pregnancies obtained after UPA treatment for fibroids in women who did not undergo surgery. There were no maternal complications related to myomas during pregnancy. All the babies were healthy. One infant had an ectopic kidney, but it was not linked to the treatment. Most deliveries were performed by cesarean section, either because of previous surgery for uterine fibroids, or in an emergency context for PE or fetal conditions. No patients experienced problems related to their fibroids during pregnancy or after delivery. Long-term follow-up has so far shown no significant regrowth of symptomatic fibroids in a large majority of women.

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REFERENCES

1. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatement before surgery. N Engl J Med 2012;366:409–20.
2. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baró F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421–31.
3. Musallam K, Tamim H, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anemia and post-operative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011;378:1396–407.
4. Williams AR, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. Int J Gynecol Pathol 2012; 31:556–69.
5. Donnez J, Vazquez F, Tomaszewski T, Nouri K, Bouchard P, Fauser BC, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014;101:1565–73.e1–18.
6. Donnez J, Donnez O, Dolmans MM. With the advent of SPRMs, what is the place of myoma surgery in current practice? Fertil Steril 2014;102:640–8.
7. Munro MG, Critchley HO, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding. Int J Gynaecol Obstet 2011;113:1–2.
8. te Velde E, Pearson P. The variability of female reproductive ageing. Hum Reprod Update 2002;8:141–54.
9. Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, et al. Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. Hum Reprod 2013;28: 2318–31.
10. Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? Hum Reprod 2002;17:1424–30.
11. Kayem G, Raiffort C, Legardeu H, Gavard L, Mandelbrot L, Girard G, et al. Specific particularities of uterine scars and their impact on the risk of uterine rupture in case of trial of labor. J Gynecol Obstet Biol Reprod (Paris) 2012;41: 753–71.
12. Dubuisson JB, Fauconnier A, Babaki-Fard K, Chapron C. Laparoscopic myomectomy: a current view. Hum Reprod Update 2000;6:588–94.

13. Jin C, Hu Y, Chen XC, Zheng FY, Lin F, Zhou K, et al. Laparoscopic versus open myomectomy—a meta-analysis for randomized controlled trials. Eur J Obstet Gynecol Reprod Biol 2009;145:14–21.
14. Kim M, Uhm Y, Kim J, Jee BC, Kim YB. Obstetrics outocmes after uterine myomectomy: laparoscopic versus laparotomic approach. Obstet Gynecol Sci 2013;56:375–81.
15. Nisolle M, Gillerot S, Casanas-Roux F, Squifflet J, Berliere M, Donnez J. Immunohistochemical study of the proliferation index, oestrogen receptors and progesterone receptors A and B in leiomyomata and normal myometrium during the menstrual cycle and under gonadotrophin-releasing hormone agonist therapy. Hum Reprod 1999;14:2844–50.
16. Islam MS, Protic O, Stortoni P, Grechi G, Lamanna P, Petraglia F, et al. Complex networks of multiple factors in the pathogenesis of uterine leiomyoma. Fertil Steril 2013;100:178–93.
17. Islam MS, Protic O, Giannubilo SR, Toti P, Tranquilli AL, Petraglia F, et al. Uterine leiomyoma: available medical treatments and new possible therapeutic options. J Clin Endocrinol Metab 2013;98:921–34.
18. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785–99.
19. Carritis S, Sibai B, Haulth J, Lindheimer MD, Klebanoff M, Thom E, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. N Engl J Med 1998;388:701–5.
20. Robson W, Leung A, Rogers R. Unilateral renal agenesis. Adv Pediatr 1995; 42:575–92.
21. Faa G, Gerosa C, Fanni D, Monga G, Zaffanello M, Van Eyken P, et al. Review morphogenesis and molecular mechanisms involved in human kidney development. J Cell Physiol 2012;227:1257–68.
22. Chai OH, Song CH, Park SK, Kim W, Cho ES. Molecular regulation of kidney development. Anat Cell Biol 2013;46:19–31.
23. Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013;120:568–74.
24. Gemzell-Danielsson K, Rabe T, Cheng L. Emergency contraception. Gynecol Endocrinol 2013;29:1–14.
25. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008;21:591–8.