We would like to discuss the mechanism of action of ulipristal acetate (UPA, marketed as ellaOne®), an orally active selective progesterone receptor modulator (SPRM) licensed for emergency contraception (EC). Each tablet contains micronized UPA 30 mg (equivalent to unmicronized UPA 50 mg) [1] and it is effective up to 120 h after unprotected intercourse.

The developers claim that UPA works by delaying ovulation and excluding any interference with embryo implantation. They based this conclusion on four experimental papers investigating the effects of UPA on ovulation [2] and on human endometrium [3–5], respectively.

These conclusions are shared by most authoritative international drug administrations. The USA FDA just adds that alterations to the endometrium might possibly contribute to UPA efficacy (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf), whereas the European Medicines Agency only mentions ovulatory delay (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001027/WC500023670.pdf). Most respected scientific societies (http://www.sigo.it/usr_files/home/guidelines.pdf) and many reviews rely completely on those conclusions [2] and report that ellaOne®, administered immediately before ovulation, significantly delays follicular rupture.

However, a careful evaluation of the same studies [2–5] leads us to question the above statements.

One paper evaluated UPA effects during the fertile period and stated that UPA can delay follicular rupture even if given immediately before ovulation, significantly delays follicular rupture.

As the fertile days are the 4 to 5 days preceding ovulation plus the ovulation day itself, we should conclude that UPA can delay ovulation only when taken in the first fertile days, whereas in the most fertile days (the pre-ovulatory day and the 2 days around it) [6], it behaves like a placebo [2].

In spite of these evident limitations, UPA effectiveness in preventing pregnancies is very high (>80%) and does not decrease depending on which of the 5 days it is taken after unprotected intercourse [1,7]. This appears surprising if we assume that UPA effectiveness is due to an anti-ovulatory action which decreases as LH levels approach to peak: we should expect a progressive reduction in its effectiveness as days elapse.

Besides, we wonder how UPA, if taken after ovulation, could delay a follicular rupture that may have already occurred up to 4 days earlier. This suggests that the effectiveness of UPA relies on other mechanisms, particularly on its endometrial effects.

Experimental studies conclude that the threshold for altering endometrial morphology is lower than that for altering folliculogenesis [3–5]. The inhibitory effect of UPA acts directly on the endometrial tissue through its inactivation of progesterone receptors [8] and is observed even after a single administration of its lowest dose.

When unmicronized UPA (1–100 mg) was administered in the mid-follicular phase, a time preceding the fertile days, all doses inhibited luteal phase endometrial maturation in a similar way. This effect was long lasting: it was observed even in the very delayed luteal phases following the coalescence of a new leading follicle and persisted until the next menstrual flow [3]. This means that all unprotected intercourse occurring in that cycle after UPA intake might end in fertilization but with no chance for implantation.

If unmicronized UPA (10–100 mg) was administered in the early luteal phase, at single doses of 1–200 mg, the highest doses, 50 mg – equivalent to ellaOne® – and 100 mg, significantly inhibited the endometrial expression of progesterone-dependent markers of luteal phase differentiation. Peripheral node addressins were significantly reduced, which is associated with implantation failure [9]. The trophoblasts, in fact, initiate implantation by binding to endometrial addressins through their own L-selectins [10].

When, at last, unmicronized UPA was administered in the mid-luteal phase, at single doses of 1–200 mg, the highest dose consistently induced early endometrial bleeding. This effect was also observed in 50% of the women treated with 50 mg, the dose equivalent to ellaOne® [5].
Thus, evidence shows that UPA endometrial effects can interfere with embryo implantation and that the high efficacy of ellaOne® in EC is probably a result of these endometrial effects, rather than the anti-ovulatory effects.

References
2 Brache, V. et al. (2010) Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. Hum. Reprod. 25, 2256–2263