ESC Virtual Seminar

Esterol/Drospirenone is a Novel efficient Contraceptive with good tolerance: Phase 3 trial in Europe and in Russia outcomes

Maud Jost, Belgium

Questions & answers

- **What do you mean by : estetrol is neutral at the liver, is ther no effect on any coagulation factor ?**
  A recent phase 2 clinical trial, comparing E4/DRSP to other COCs containing EE/LNG or EE/DRSP after 3 and 6 cycles, showed changes in hemostasis parameters after treatment with E4/DRSP that were smaller or similar to those observed for EE/LNG. More pronounced differences were observed versus EE/DRSP, i.e. effects of E4/DRSP were smaller, supporting the hypothesis that the effect of COCs on hemostasis parameters is mainly mediated by the estrogenic component (Douxfils et al. 2020, Contraception).
  In addition, the more neutral impact on the liver has also been observed with other liver parameters, like angiotensinogen, cortisol binding globulin (CBG) and thyroxin binding globulin (TBG), for which the increase with E4/DRSP was significantly lower compared to EE/LNG and EE/DRSP. Previous observations have shown that E4 slightly increases sex hormone binding globulin (SHBG). In this study, EE/LNG and E4/DRSP had a limited effect on SHBG while EE/DRSP increased SHBG substantially, which suggests that E4 in combination with DRSP has a low estrogenic effect, in particular on the liver (Klipping et al. 2021, Contraception).

- **What is a difference between metrorrhagia and vaginal haemorrhage**
  The term vaginal haemorrhage is a MedDRA preferred term used for the verbatim of vaginal bleeding when there was no specification of timing of bleeding or metrorrhagia was not specified.

- **When is this product expected in the UK?**
  This COC containing E4 15 mg/DRSP 3 mg is expected to be available in UK in the coming months depending on the MHRA review.

- **Are there any contraindications like VTE in the family?**
  Clinical phase 2 data showed that the changes in hemostasis parameters after treatment of E4/DRSP were smaller or similar to those observed for EE/LNG, and less pronounced versus EE/DRSP, which supports the hypothesis that the effect of COCs on hemostasis parameters is mainly mediated by the estrogenic component (Douxfils et al. 2020, Contraception). In the Phase 3 program, which aimed to

assess efficacy and safety in a large group of individuals, one venous thromboembolic event occurred in more than 3,500 women while one would expect more VTE events in a phase 3 program.
However, additional data and Phase 4 studies are required to assess the incidence of VTE, even more in at-risk population. Currently, the contraindications for COCs are applicable to the use of E4/DRSP.

- **Is it possible to treat l dysmenorrhea with E4/drosperinone?**
  It is an interesting question to look at dysmenorrhea as an indication for a low dose estrogen/progestin. The phase 2 and phase 3 clinical studies performed were not done with the intend of looking primarily at dysmenorrhea. However, it is interesting to note there was a low incidence of drug-related adverse events linked to dysmenorrhea: only 2.4% treated with E4/DRSP reported adverse effects related to dysmenorrhea, and only 0.2% discontinued due to abdominal pain, not necessarily related only to dysmenorrhea.

- **E4/drospirenon could it be a good option for patients suffer from decreased libido and mood change**
  Pooled data of two phase 3 trials showed a low incidence of reported adverse events related to mood swing and a decreased libido. Moreover, discontinuation rate due to mood changes in the entire population was <1% and 0.5% due to decreased libido. Whether E4/DRSP is a good option for this specific target population should be further investigated in phase 4 trials.