Confounding by indication
We stated that in the past there has been a general tendency to prescribe the most recently introduced OCS to women thought to be at increased risk of VTE. In a former publication6 Lidegaard has agreed: “In many countries including Denmark, many gynecologists and general practitioners have prescribed these new pills to women at anticipated increased thrombotic risks”. He has also stated that the risk of VTE is significantly disposed to smoking, and years of schooling are probably the most important confounders to adjust for to account for prescribing bias.

Study size
We repeat that in the presence of systematic bias, a large study will more readily produce statistically significant results than a small one. Statistical significance, however, does not equate causation, and in a large study a biased or confounded association may nevertheless be “significant”.

Conclusion
We are aware that ex-post facto criticism of studies conducted by others is easier than doing better oneself. We would welcome an opportunity to discuss with Professor Lidegaard details of additional subanalyses that might shed light on the mechanisms of this publication, and in this correspondence. However, we reiterate that in our view the Danish comparison of selected progestogens with LNG was not valid.

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References

LNG may still be the best oral EC option
The last two issues of this Journal each included a commentary1–2 on the progestrone receptor modulator (PRM), ulipristal acetate (UPA). Both commentaries concluded that UPA is more effective for emergency contraception (EC) than levonorgestrel (LNG). Now, as the key studies have been published, we are able to assess the possible merits of providing UPA rather than LNG oral EC.

At present there remain good reasons to be cautious about claims that UPA is the superior emergency contraceptive.

1. Both studies comparing LNG and UPA found no significant difference in pregnancy rates when used for EC. The recently published randomised controlled trial (RCT)3 was designed as a non-inferiority study and a previous RCT4 also showed non-inferiority for UPA. None of the studies were powered for secondary outcomes as to which is the better method of EC. There are two reasons why a non-inferiority design was chosen: (i) it is cheaper as a smaller sample size is required and (ii) it is all that is required for drug licensing. Analysis of the combined data of both studies showed that UPA showed significantly reduced pregnancy rates for UPA as compared to LNG. A meta-analysis does not replace a sufficiently powered single study such as the World Health Organization (WHO) multicentre RCT.5 The WHO study also compared a PRM (10 mg mifepristone) with LNG. It was powered to find a difference of one pregnancy between the two groups.

2. The primary outcome of the recently published RCT3 was pregnancy rate, which was not statistically different for LNG and UPA. Pregnancy risks in the LNG arms of the recently published RCT.3 It showed non-inferiority for UPA. None of the studies were powered for secondary outcomes.

3. At present there remain good reasons to be cautious about claims that UPA is the superior emergency contraceptive. There are two reasons why an RCT comparing LNG and UPA will not be sufficient for assessing the relative merits of LNG and UPA for EC. First, because of the smaller sample size required for the non-inferiority design, the study will have insufficient power to detect a difference of one pregnancy. Second, because of the difference in design, the study will be unable to assess the possibility that the combination of a progestogen and a PRM at the same time might cancel each other out. As the use of hormonal contraception was specifically excluded in the recruited population, it is not possible to speculate how UPA and hormonal contraception affect each other. The serum half-life of UPA may only be 32.4 hours6 but its biological effects last a lot longer. When the average ovulation period it prevents ovulation for 5 or more days in 59% of cases.7 Similarly, it might affect the effectiveness of hormonal contraception for an uncertain period of time. While we know that there are no adverse interactions between LNG and hormonal contraception, we cannot even estimate the effect of UPA on the effectiveness of ‘quickstart’ hormonal contraception and vice versa.

3. UPA is a cousin of mifepristone, and it is at least conceivable that women may access it under the pretext of EC, possibly by terminating an early pregnancy. UPA (30 mg) (ellaOne®) taken as EC does not appear to interrupt a pregnancy, and the same number of PRM pregnancies occurred in the LNG and UPA arms of the recently published RCT.7 It will, however, not be long before it will become common knowledge that to get more than one dose of ellaOne one will need to present to more than one clinic. This may be an attractive proposition for women who cannot access a termination on the National Health Service. A drug that can induce abortions would also have a real value on the black market. To prevent this we should consider pregnancy testing prior to administration of ellaOne under direct supervision.

The purpose of EC is to prevent unplanned pregnancy. In most cases this can best be achieved if EC can be combined with ongoing contraception. As this has not been studied we do not know how the combination of UPA and hormonal contraception will affect the effectiveness of EC or ongoing contraception. At least the combination of LNG and UPA might be cheaper and more effective in preventing pregnancy, as the use of LNG EC would reduce the effectiveness of UPA.8

3. Even now for the purpose of pregnancy prevention of unplanned pregnancies presenting for EC, LNG plus ‘quickstart’ DMPA remains the most evidence-based approach for women who do not wish to have an intrauterine device fitted.

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References
Letters to the editor


Reply

In response to the letter1 from Drs Pittrof, Rubenstein and Sauer we would like to make the following points:

1. There is clear evidence that ulipristal acetate (UPA) is more effective than levonorgestrel (LNG). Biomedical studies have shown that when given at mid-cycle (when risk of pregnancy is greatest), UPA is able to delay ovulation whereas LNG is no better than placebo.2,3 Studies have also demonstrated that UPA has endometrial effects (which may or may not contribute to its efficacy) whereas LNG does not.4,5 The recent randomised controlled trial and meta-analysis of studies comparing UPA with LNG for emergency contraception (EC) that we published in the Lancet showed that UPA reduces the risk of pregnancy by almost one half compared to LNG.6

2. A Cochrane review actually concluded that mifepristone with an ipiemislidose >25 mg) were significantly more effective than LNG for preventing pregnancy when used for EC.7

3. As regards the possible effect of UPA if taken in early pregnancy, we observed in our study that there were pregnancies in women treated with UPA that were judged to have occurred well before treatment, that continued after UPA treatment had ended.8 Furthermore, the miscarriage rates in women who received UPA was similar to that in women who had LNG and no different from that observed in the general population of pregnant women.9 Whilst there have been a small number of non-normal births in women who received UPA, clearly UPA is a new drug and so it is only appropriate that a European pregnancy registry has been established to collect more information on effect on ongoing pregnancy.

4. We discussed the possible interaction of a progesterone receptor modulator (PRM) with hormonal contraceptive methods in our commentary on this Journal1 and concluded that further research is required, because the requirement to abstain or use barrier methods for the remainder of the menstrual cycle is not realistic. The miscarriage rates in women who received UPA from our commentary, even for a pilot study, is a description for this study that is hidden in the discussion. It is stated that the study was prospective, though the description of the data collection is not adequate to support this. We feel that a study conducted over the Christmas period, when workload is not typical, for such a short period of time may not truly reflect patient flow. In fact the observed improvement may not be related to the change in process at all. Also, evaluating such a change immediately is unlikely to record the true effect of the change. Finally, in relation to the methods used in the study, the practice of discarding incomplete forms will introduce further bias and compiles the statistics.

In conclusion, we welcome a paper that aims to inform patients at the centre of the care, studying ways to reduce waiting time, but would guard against overenthusiastic claims.

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References


Combined pill and GTD

I have read the new UK Medical Eligibility Criteria for Contraceptive Use (UKMCC) guidelines1 and am surprised and concerned that the recommendations regarding hormonal contraception, particularly the combined oral contraceptive pill (COC) and gestational trophoblastic disease (GTD), have been changed. It used to be recommended that the COC was not taken until the beta-humoral chorionic gonadotropin (beta-hCG) levels had fallen to normal following evacuation of a hydatidiform mole.2 The new (2009) guidelines state the COC can be started whilst the beta-hCG levels are decreasing, persistently elevated and in the presence of malignant disease. The accompanying notes suggest that starting the COC in this situation may decrease the requirement for chemotherapy (by promoting a more rapid reduction in beta-hCG levels). This advice differs to that given by the Royal College of Obstetricians and Gynaecologists (RCOG), the Patient UK website (a common source of information for both general practitioners and patients) and the Charing Cross Hospital gestational trophoblastic neoplasia (GTN) website, which recommend that hormonal methods [and intrauterine devices (IUDs)] are not used until the beta-hCG level has returned to normal. I am puzzled by the new advice given by UKMCC.

The guidelines given in the 2009 guidelines all predate, and are very similar, to those in the 2006 guidelines. Why has the advice changed? I am unaware of the paper Contraception3 suggesting that both the COC and IUDs can be used in women with GTN. This paper also quotes some publications suggesting that COC use reduces the risk of women developing post molar trophoblastic disease, however it is not quoted by UKMCC 2009.

Professionals and patients become confused when contradictory advice is given. As a specialist we should be more aware of this than most following the problems that have arisen after various ‘pill scares’. I would be interested to hear why UKMCC have changed their guidance but

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