

adjustment using time-trend data as a surrogate for obesity could possibly have reduced confounding, but it would not have eliminated it, especially since its effect in combination with other risk factors is multiplicative.

With regard to possible confounding from other sources, VTE was more frequently diagnosed in women who only completed primary school. Socioeconomic status was thus a determinant of VTE risk, and the possibility that this factor may have reflected detection bias was not evaluated. With regard to other potential confounders Lidegaard mentioned that allowance for treated diabetes, heart disease, hypertension and hyperlipidaemia did not affect the findings. Only heart disease and diabetes are risk factors for VTE; hypertension and hyperlipidaemia are not. As for other factors, the Danish study did not evaluate potential confounding due to a family history of VTE, recent surgery, trauma or immobilisation.

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 conferred by "Family disposition, BMI, 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 issues raised in his 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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LNG may still be the best oral EC option

The last two issues of this Journal each included a commentary^{1,2} on the progesterone 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, it is possible to assess the possible merits of providing UPA rather than LNG oral EC.

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

- 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 to provide the answer 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 but did not find one.
- The primary outcome of the recently published RCT³ was pregnancy rate, which was not statistically different for LNG and UPA. Pregnancy prevention rates are listed on ClinicalTrials.gov (No. NCT00551616) as a secondary outcome. The results were presented at a conference⁶ but were not reported in the recent publication.³ Pregnancy prevention rates are not observed but calculated and are much less robust than pregnancy. In theory, randomisation should have ensured that pregnancy risks in the LNG and UPA groups will have been similar, and different pregnancy prevention rates should also be apparent in different pregnancy rates. As we do not know if a power calculation was performed for secondary outcomes we cannot assess the likelihood of a type 1 error (i.e. finding something which is not there).

Even if UPA is more effective than LNG for EC used under trial conditions, there are good reasons (costs aside) to remain cautious about the use of UPA:

- Post-implantation use of LNG has not been associated with any harm to an early pregnancy. This still needs to be shown for UPA.
- Information provided on ClinicalTrials.gov (No. NCT00551616) explains that the recent³ study specifically excluded women who intended to use hormonal or used contraception during the current cycle. While the same criteria were used for the WHO multicentre trial⁵ it is unlikely that the use of hormonal contraception started at the

time of LNG EC would reduce the effectiveness of EC or vice versa. This is important as there is a high risk of subsequent conception in the current cycle in women receiving EC.⁷ In a commentary in the January 2010 issue of this Journal, Cameron and Glasier⁸ appear to suggest that hormonal contraception can also be started at the time of UPA EC. This may not be the case, as there are at least theoretical reasons why 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 recent RCT it is only possible to speculate how UPA and hormonal contraception affect each other. The serum half-life of UPA may only be 32.4 hours⁹ but its biological effects last a lot longer. When given in the immediate pre-ovulation period it prevents ovulation for 5 or more days in 59% of cases.¹⁰ 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 with the intention of terminating an early pregnancy. UPA (30 mg) (ellaOne®) taken as EC does not appear to interrupt a pregnancy, and the same number of pre-EC pregnancies occurred in the UPA and LNG arms of the recently published RCT.³ 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 for the combination of EC with LNG with an immediate depot medroxyprogesterone acetate (DMPA) start there is strong evidence of reduced pregnancy rates.¹¹ Even now for the purpose of prevention of unplanned pregnancy in women 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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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 mid-doses of mifepristone (>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.⁶ Furthermore, the miscarriage rate 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. Whilst there have been a small number of 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 contraception in our commentary in this Journal⁸ and concluded that further research is required, because the requirement to abstain or use barrier methods for the remainder of the month is not evidence based.
5. Drs Pittrof, Rubenstein and Sauer express concern that women who cannot access National Health Service abortion services may try to procure several doses of UPA from different clinics with the intention of trying to induce an abortion (unproven effect), or sell the product on the 'black market' at 'real' value. This course of action seems unlikely since a woman could more

easily purchase an effective treatment (mifepristone and misoprostol) over the Internet, at an affordable price (www.womenonweb.org).⁹

As we discussed in our commentary⁸ in this Journal, UPA does by virtue of the fact that it is a PRM raise issues for service delivery and for 'bridging' contraception. However, in spite of these challenges, we believe that contraceptive service providers will judge the evidence for themselves, and welcome UPA as an advance in EC that is more likely to help women avoid an unintended pregnancy than LNG.

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Self-triage and clinic waiting times

We would like to thank Drs Hitchings and Barton¹ for concluding that self-triage can effectively reduce clinic times as in our clinical experience this appears to be the case. Their paper describes a significant reduced waiting time from 40 to 23 minutes (expressed as median).¹ However, we are unsure if the methods used in this survey are robust enough to conclude this.

First, the paper does not clearly define its research question;² this then impacts on the methods it uses. For example, if the research question was "Does self-triage reduce waiting times?" then a method that measures waiting time would have been more appropriate. Alternatively, a questionnaire would have been better if the paper set out to find out "Is self-triage acceptable to patients in SRH?"

Whilst acknowledging that the ideal methodology may not have been possible, we do think the actual design of the survey could have been improved. The original power calculation is not included, so it is not clear if the sample is adequate to demonstrate a significant result. This calculation is important even for a pilot study, a descriptor 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 complicates the statistics.

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

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Combined pill and GTD

I have read the new UK *Medical Eligibility Criteria for Contraceptive Use* (UKMEC) 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-human chorionic gonadotropin (β -hCG) levels had fallen to normal following evacuation of a hydatiform mole.² The new (2009) guidelines state the COC can be started whilst the β -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 β -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 β -hCG level has returned to normal.

I am puzzled by the new advice given by UKMEC. The references given in the 2009 guidelines all predate, and are very similar, to those in the 2006 guidelines. Why has the advice changed? I am aware of the paper in *Contraception*³ 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 UKMEC 2009.

Professionals and patients become confused when contradictory advice is given. As a specialty 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 UKMEC have changed their guidance but