Individualising oral hormonal contraceptive regimes through mathematical modelling

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Introduction

Aim: can we use mathematical modelling to personalise oral contraceptive doses regimes?

Oral contraceptive pills are the most widely used form of birth control in Australia [1]. However, these medications remain surprisingly poorly understood, with dosages of active ingredients varying significantly despite known negative side effects from overmedication [2].

Methodology

- My model considers a contraceptive based on Femme-Tab ED 20/100, a commonly used combined pill in Australia, which uses levonorgestrel (LVG) as the progestin and ethinyl estradiol as the estrogen.
- For each hormone, I used a two-compartment model fitted to the pharmacokinetic parameters available in the literature [3,4] which feeds into an existing mathematical model of the menstrual cycle [5,6].

Results

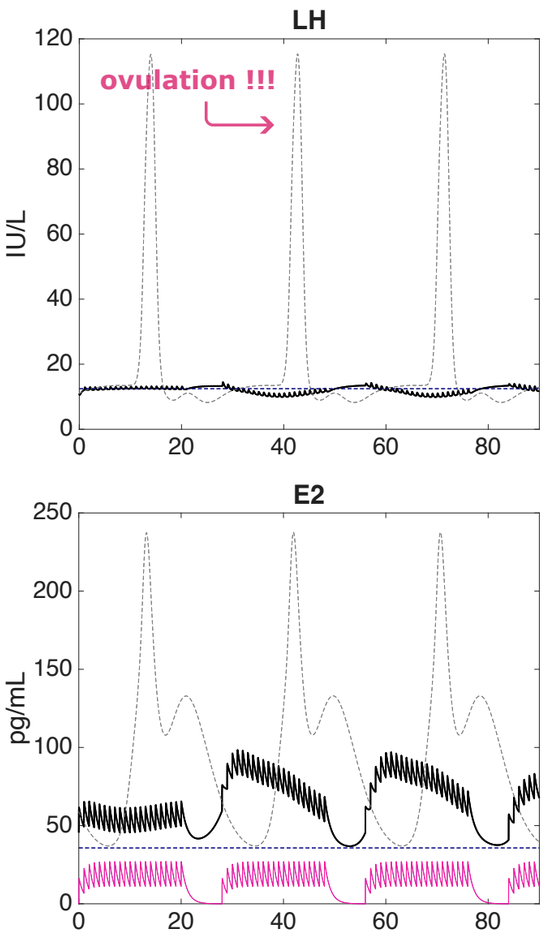

Figure 1: LH (top) and estradiol (bottom) concentrations over 90 days. The black line denotes the model output for a typical dosing regimen, the dashed grey line the model output with no exogenous hormones and the purple line the equivalent concentrations of exogenous estradiol

Figure 1 shows a simulation of a typical schedule of 21 active pills, followed by 7 inactive pills. Our results match experimental data [3,4]:

- The luteinising hormone (LH) surge is fully suppressed, indicating a contraceptive state.
- The inactive pills allow rising estradiol and progesterone levels every 28 days, replicating 'natural' periodic fluctuations.

Using this model, if we can determine parameter profile for a given patient, we can determine the minimal dose of the drug to induce contraception. **Figure 2** provides an example of what is possible:

- I chose to vary the half-life of levonorgestrel, which is known to take values between 20-60 hours depending on the patient [4].
- We use the model to find the minimal dose of the drug which induces a contraceptive state.
- Our results suggest that the usual dosage is over double the minimal dose required for our median patient.

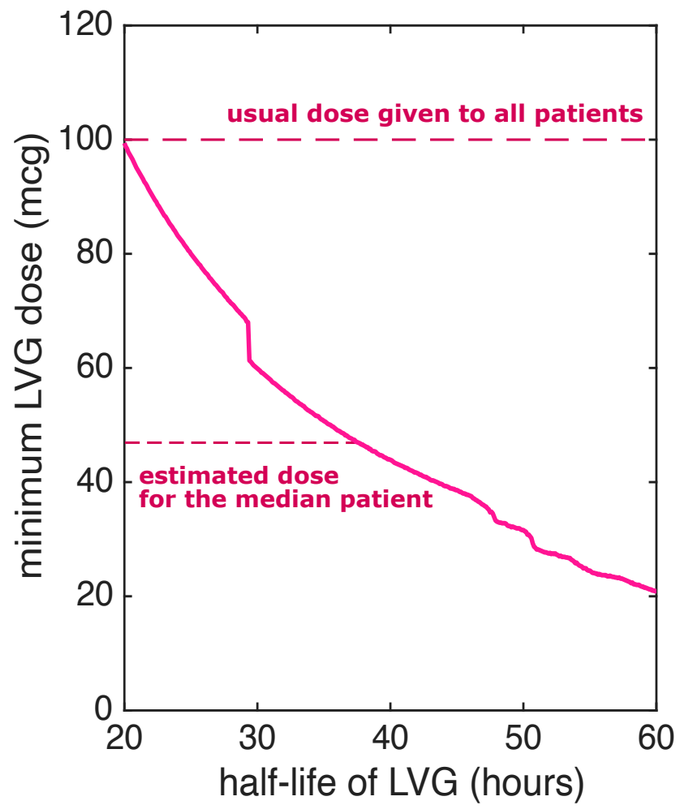

Figure 2: The minimum dosage of levonorgestrel (combined with 20mcg of ethinyl estradiol in a 21 days on / 7 days off schedule) required to induce contraception. A contraceptive state has been defined as LH concentrations remaining below 40IU/L over a simulation running for 300 days.

Conclusion

While this model suggests that individualising contraceptive dosages is possible there are some significant barriers that must first be overcome:

- Primarily, there is a lack of data for fitting every part of this model. This makes it difficult to many judgements about the variability and significance of many of the parameters
- This is made worse by the fact many of the parameters in the menstrual cycle model are not biologically motivated. The parameters are therefore very difficult if not impossible to measure directly, requiring the model to be reframed before it would be possible to fit to an individual's data.

We have demonstrated that this model replicates reality and can be used to inform personalised dosage regimes. Furthermore, this model can easily be extended to non-oral forms of hormonal birth control, and can even be used to study treatments for some diseases related to ovarian hormone levels, such as endometriosis and polycystic ovarian syndrome.

References:

Uterus icon from Flaticon.com
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