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Women's Health: Maximizing Study Design of Combined Oral Contraceptives Drug Interaction Studies

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A CDC survey of women between 15-49 years old found that nearly 13% use oral contraceptives [1]. Most birth control pills on the market contain two key synthetic hormones, a progestin and an estrogen, typically ethinyl estradiol (EE), and are known as combined oral contraceptives (COC). Both progestins and estrogens are highly metabolized by phase I and phase II pathways, which may lead to serious drug-drug interactions (DDI) when taken with other medications. Specifically, when co-administered with inducers of metabolizing enzymes like cytochrome P450 (CYP)3A, CYP2C, uridine 5'-diphospho-glucuronosyltransferases (UGTs) or sulfotransferases (SULTs), there is the potential that progestin and EE may lose efficacy resulting in unintentional pregnancy. For instance, strong CYP3A inducers can upregulate activity of CYPs and phase II enzymes through pregnane X receptor and androstane receptor regulation, which may result in biotransformation of progestins and significant reduction of exposure to EE and progestins by nearly 50% [2]. Meanwhile, strong inhibitors of CYPs, UGTs and SULTs could increase the exposure of progestins and estrogens. As an example, EE exposure above levels equivalent to a 50 µg dose may increase the risk of venous thromboembolism (VTE), a condition resulting in blood clots that can lead to stroke (reviewed in [2]).

Choice of COC

There are several progestins and estrogens on the market (Table 1), that have different metabolic pathways and their DDI magnitude of effect can vary. In a head-to-head comparison study of 5 common progestins, rifampicin dosed at 600 mg/day as a strong CYP3A inducer in postmenopausal women resulted in >80% reduction in exposure of dienogest (DNG), desogestrel (DSG) and drospirenone (DRSP), with smaller decreases for levonorgestrel (LNG) and norethindrone (NET) [3]. This study should not undermine the impact of strong CYP3A inducers on progestins like LNG and NET. A 2018 survey of COC DDI studies found >40% reduction in LNG, NET and norgestimate (NGM) as well as EE exposure when co-administered with a variety of strong CYP3A inducers [2].

On the other hand, progestins and EE are generally less sensitive to CYP3A inhibitors with the exception of DRSP. Strong CYP3A inhibitors can elevate DRSP area under the curve (AUC) by nearly 50% to >2-fold. For example, ketoconazole, an antifungal agent, increases DRSP exposure by 170% [2]. While moderate CYP3A inhibitors typically result in a modest increase on LNG and NET AUCs, this is not always the case. Atazanavir, an HIV antiviral and moderate CYP3A inhibitor, interestingly demonstrated a robust effect on NET and EE exposure, increasing their AUCs by nearly 110% and 50%, respectively (reviewed in [2]). Thus, the atazanavir drug label recommends caution when co-administering with oral contraceptives, specifying EE concentration limits and warning about the potential increased safety risks of chronic elevated progesterone exposure [4].

In the US, the most common progestins include NET, NGM, LNG and DRSP and are generally considered for a COC DDI study. More recently, there is renewed interest in 17β-estradiol (E_2) [5] or estradial valerate (E2V) for contraception. Recent data demonstrated that E2 and E2V have similar efficacy and cycle control as EE-based COCs and should also be considered for DDI potential.

Table 1. Metabolism of Oral Contraceptive Hormones

Contraceptive Hormone	Phase I Metabolizers	Phase II Metabolizers
Estrogens		
Ethinyl estradiol (EE)	CYP3A4 (major), CYP2C19, CYP2C9 and CYP2B6	SULTE1 (major) and UGT1A1 (minor)
Estradiol valerate (E2V)	CYP3A4, CYP2C19, and CYP2B6	UGTs
17β-estradiol (E_2)	CYP1A, CYP1B, and CYP3A	
Progestins		
Desogestrel (DSG)	CYP2C19 and CYP3A4	
Dienogest (DNG)	CYP3A4	
Drospirenone (DRSP)	CYP3A4, reductase and esterase	UGTs and SULTs
Levonorgestrel (LNG)	CYP3A4	UGTs and SULTs
Norethindrone (NET)	CYP3A4 and CYP2C19	UGTs and SULTs
Norgestimate (NGM)	CYP3A4	UGT1A1
Norgestrel (NG)	CYP3A4	
Nomegestrol acetate (NOMAC)	CYP3A3, CYP3A4, and CYP2A6	

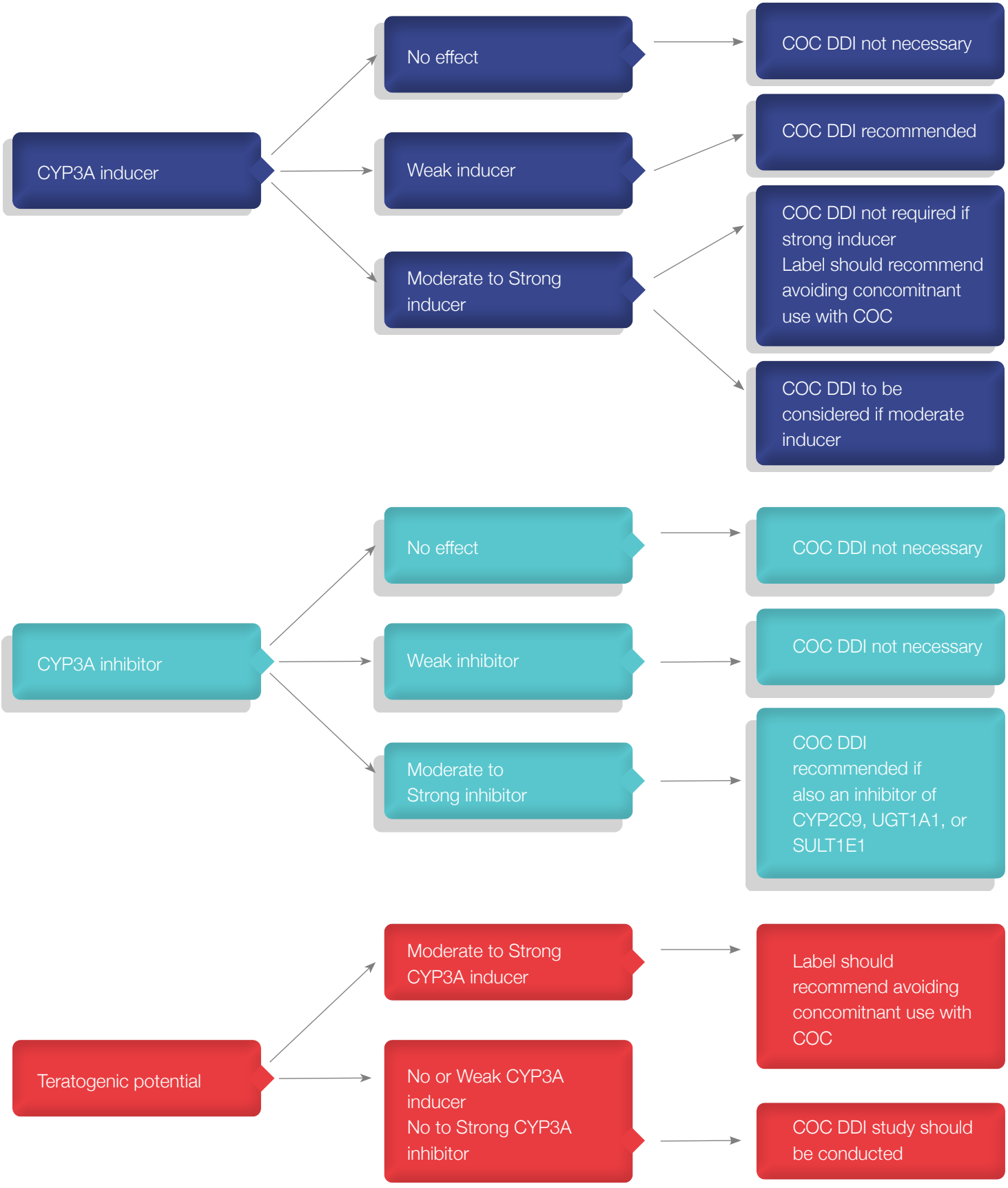
Adapted from [2, 6-8].

Most progestins, except for NGM and DRSP, bind to sex hormone-binding globulin (SHBG) once in circulation, and total exposure correlates with SHBG levels. Moreover, as a synthetic hormone, EE administration induces SHBG production in the liver contributing to this progestin PK characteristic (reviewed in [7]). For COC DDI studies, multiple cycles of COC may be recommended based on the progestin, and steady state accumulation of progestin may be anticipated resulting in nonlinear PK profile.

Regulatory Guidance for COC DDI Studies

In November 2020, the FDA issued draft guidance Clinical Drug Interaction Studies with Combined Oral Contraceptives [9], to help mitigate the risk of potential drug interactions of investigational products on COCs. The guidance focuses on the impact of CYP3A sensitive products. Not covered in the document are DDI recommendations for transdermal contraceptives however, a DDI study with a COC could inform other types of contraceptives with the same progestin. Nonetheless, the guidance provides a helpful decision tree when a COC DDI should be considered and/or if the label should indicate contraindicative use, as summarized in Figure 1. Sponsors should review results from previous in vitro or clinical CYP DDI studies with a CYP3A sensitive substrate such as midazolam to inform the necessity of a COC DDI study.

Figure 1. Recommendations for a COC DDI Study with CYP3A Inducing and Inhibiting Investigational Drugs



Adapted from draft guidance [9].

The guidance recommends common progestins such as NET, NGM, LNG or DRSP for COC DDI studies [9]. In practice, such DDI studies would require a sample size of around 24 subjects, yet given the higher variability in PK for DRSP, DDI studies with DRSP would require more subjects. The guidance also indicates that DRSP may be used as a worst-case scenario for CYP3A inhibition and results may be extrapolated to NET and LNG with FDA approval and prior discussion [9].

Study Design Considerations

DDI studies with COCs are commonly conducted in populations of premenopausal adult females under the age of 45 as a safeguard due to the increased risk of DVT, but when administered as single-dose or with teratogenic compounds can also be performed in a postmenopausal female cohort. Pharmacodynamic (PD) endpoints, however, can only be evaluated in premenopausal females and under multiple dose conditions. Typically, we recommend COC-naive women for a COC DDI study. This group is readily feasible to recruit compared to the increased challenge to recruit and conduct a study whereby women washout from their current contraception to ensure that their cycles are synchronized.

The study design can include administration of a single dose or a full 28-day cycle (21 days active + 7 days inert pills) of COC. The investigational product (IP), being the perpetrator drug, is typically dosed at the highest proposed therapeutic dose, given either as multiple doses to steady-state for an inhibition effect or multiple doses up to 14 days for an induction effect. Key to determining the dosing regimens for both COC and IP are the drug class of the IP and its PK characteristics as well as the type of anticipated interaction between the drugs, especially based on the results of a prior DDI study with midazolam as CYP3A victim. Single dose or full cycle COC PK-only studies without PD components may be considered as a default approach for oral contraceptive DDI studies [7]. PD assays such as luteinizing hormone, follicle-stimulating hormone, and progesterone can add supportive information and would require multiple doses of COC administered. Based on EE (20 hrs) and progestin (20-35 hrs) half-lives, we typically recommend 96-120 hrs and 120 hrs PK sampling for EE and progestin respectively, and 7 day minimum washout period. While not an exhaustive list, Table 2 provides some examples of study designs for various scenarios.

Table 2. Combined Oral Contraceptive Drug Interaction Study Design Examples

Study Type	Study Design	Period 1	Period 2
PK-only, induction study	Fixed-sequence, 2-period study, single dose COC, multiple dose IP	Day 1: single dose COC, 120 hrs PK sampling. Followed by 7 days washout.	Day 1-18: administer IP Day 14: administer single dose COC, 120 hrs PK sampling.
PK-only, inhibition study	Fixed-sequence, 2-period study, single dose COC, multiple dose IP	Day 1: single dose COC, 120 hrs PK sampling. Followed by 7 days washout.	Day 1-12*: administer IP Day 8*: administer single dose COC, 120 hrs PK sampling.
PK-only or PK/PD study	Fixed-sequence, 2-period study, multiple dose COC and IP	1 cycle of COC (Days 1-28), 24 hrs PK sampling on Day 21. No washout.	1 cycle of COC (Days 1-21), co-administer IP Days 1-21 of cycle, 24 hrs PK sampling on Day 21.
PK-only or PK/PD study, continuous COC	Fixed-sequence, 2-period study, continuous COC and multiple IP	Days 1-21: COC once daily, 24 hrs PK on Day 21. No washout.	Days 1-10* (or Day 1-14): co-administer COC and IP, 24 hrs PK sampling on Day 10 (or Day 14)

Reciprocal DDI study	Fixed-sequence, 2 period study, multiple dose COC and IP	Days 1-7*: IP alone, 24 hrs PK collection on Day 7*. No washout.	1 cycle of COC (Days 1-21)** with IP co-administered for 7* days (Days 15-21 of cycle), 24 hrs PK collection on Days 14 and 21 for COC, 24 hrs PK collection on Day 21 for IP.

**to be updated based on IP reaching steady-state levels. ** to be updated based on the selected progestin.*

There is no significant DDI effect if the 90% confidence intervals for the geometric mean AUC and Cmax ratios fall within 80-125% boundaries. If these values are outside the no-effect boundaries, then the totality of evidence should be considered when determining a DDI effect. Moreover, if EE exposure increases to what would be observed following a 50 µg dose during the DDI study, the label should recommend avoiding concomitant use with COC. On the other hand, if a decrease in progestin or EE exposure is observed during the DDI study, the label should recommend back-up or alternative contraceptive methods.

Multi-Part and Adaptive COC DDI Studies

More recently, sponsors are seeking multi-part and adaptive designs that also incorporate COC DDI with key labeling studies such as the interaction with other CYP substrates or transporters. A multi-part or adaptive study requires only one protocol and streamline the start-up process. A CRO with extensive experience will foresee and plan for any design and enrollment barriers, for example by using a multi-part design running in parallel to reduce the study duration. At Celerion, our team of protocol scientists will propose optimal PK sampling timepoints and appropriate I/E criteria for a successful study.

Bioanalytical Support for COC DDI Studies

Prior to 2000, EE and progestin PK analysis were plagued with high variability, making interpretation of DDI results difficult. This was mainly attributed to the radioimmunoassay method applied [10]. More sophisticated gas or liquid chromatography mass spectrometry (GC/MS or LC/MS) technology have drastically improved assay variability and data quality. A review of 17 clinical studies investigating the PK of 150 µg LNG and 30 µg EE in a COC found less than 20% variability (CV%) for several LNG and EE PK parameters [10]. Another key bioanalytical consideration is the level of detection. Celerion utilizes advanced liquid chromatography with tandem mass spectrometry (LC/MS-MS) for progestin and EE analysis, with a large range of detection (Table 3.)

Table 3. Celerion's Bioanalytical Validated COC Assays

COC Component	Technique	Matrix	Range	Sample collection tube anti-coagulant
Ethinyl Estradiol	LC-MS/MS	Human Plasma	2-500 pg/mL	EDTA
Drospirenone	LC-MS/MS	Human Plasma	0.5-50 ng/mL	EDTA
Levonorgestrel	LC-MS/MS	Human Plasma	50-10000 pg/mL	EDTA
Norethindrone	LC-MS/MS	Human Plasma	0.05-10 ng/mL	K2 EDTA
Norgestimate; Deacetylnorgestimate	LC-MS/MS	Human Plasma	20-2500 pg/mL	EDTA
Norgestrel (reported as Levonorgestrel)	LC-MS/MS	Human Plasma	0.05-10 ng/mL	EDTA, Heparin

Adapted from Celerion's Bioanalytical Validated Assay List.

Conclusion

The recent FDA draft guidance stresses the consequences of DDI effects on COCs, especially unintentional pregnancy and risk VTE [9]. However, other undesirable affects such as headache, nausea, breast tenderness and spotting between menstruation cycles are also worth noting and have been reported when progestin or EE concentrations are altered [11]. New drugs in development intended for young female populations that exhibit CYP3A induction or inhibition are likely candidates for a COC DDI study. There are several study design options available including single dose, multiple doses as well as adaptive studies to assess a COC DDI effect safely and efficiently.

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