Drug interaction with Oral Contraceptives-
considerations for study design and data interpretation

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Disclosures

- Haiying Sun and Venkateswar Jarugula are full time employees of Novartis Institutes for BioMedical Research, East Hanover, NJ
- Haiying Sun and Venkateswar Jarugula are stockholders in Novartis

Outline

- Clinical relevance of oral contraceptives (OCs) drug-drug interactions
- Oral Contraceptive use world-wide
- Drug metabolism characteristics of Oral Contraceptives
- Sex Hormone Binding Globulin (SHBG) and its effect on OCs
- PK/PD based OC DDI study-case example
- NCE impact on progestins
- Review of labeling information
- Summary of study design and interpretation considerations

Information considered to initiate clinical OC DDI study

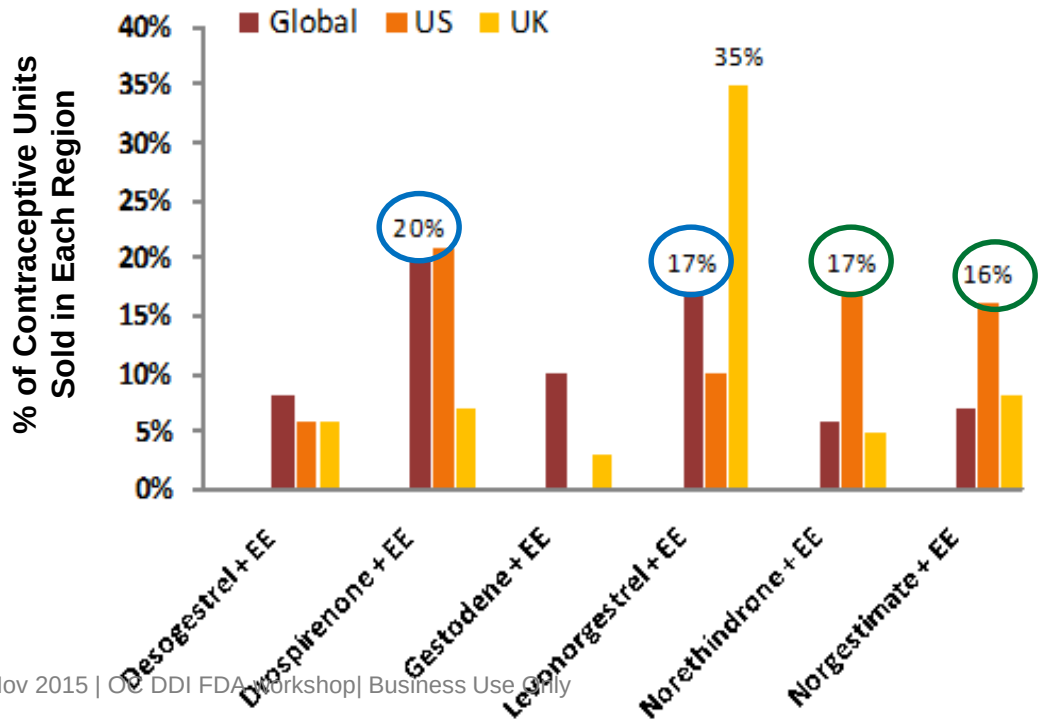
OCs as victim drugs

- Clinical program considers the Benefits/Risks when including women of child bearing potential
  - especially when reproductive toxicity studies are not completed or compound is teratogenic
- The level of contraception (highly/acceptable effective) depends on reproductive toxicity and genotoxicity of the NCE
- Whether OC can be used as one of the contraceptive method depends on DDI assessment outcome

- Understanding of ***in vitro*** findings
  - DDI potential of NCE (CYP3A4/ UGT1A1/CYP2C19/CYP2C9)
- A consideration of ***in vivo clinical*** DDI findings
  - Eg In vivo CYP3A4 probe study with Midazolam, if available
- A consideration of teratogenic findings
  - *A potential human teratogen needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of in vitro induction study results.*

Use of COCs Worldwide

- **Ethinyl estradiol** is the common component of most COCs
- **Progestins:**
  - **Global total: Levonorgestrel and drospirenone are most commonly used**
  - Regional differences exist:
    - **USA – Norethnidrone and norgestimate more commonly used than in other countries**
    - China – Desogestrel (73% of total volume)
    - Italy – Gestodene (33% of total volume)



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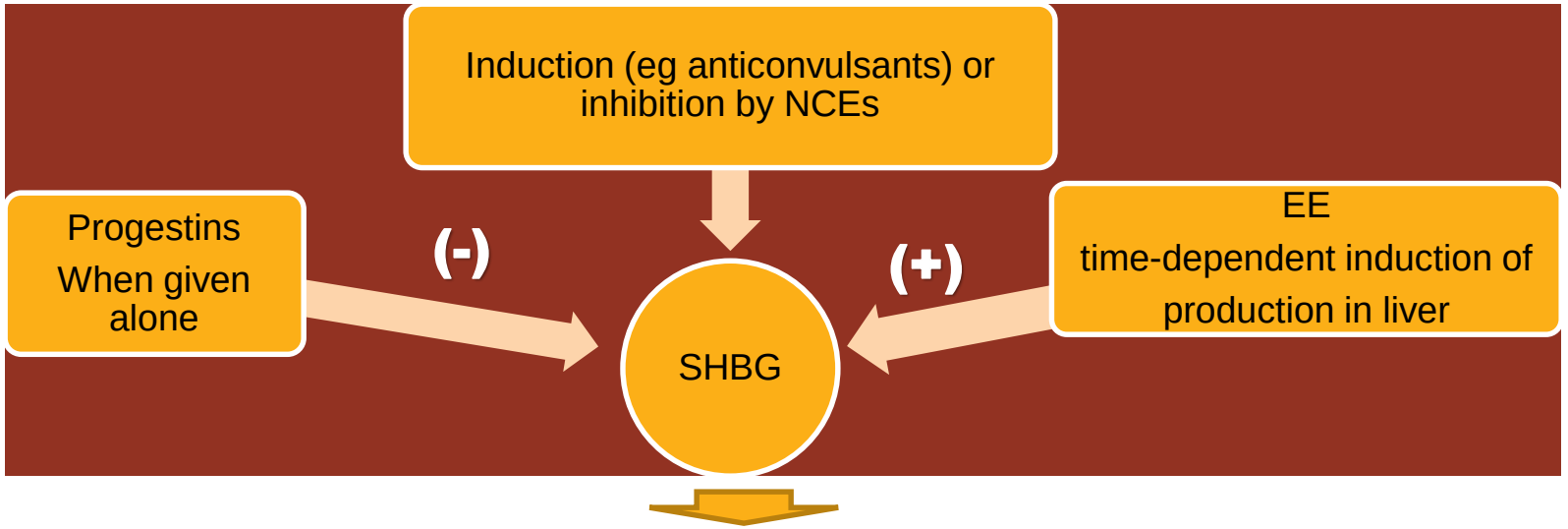
Drug Metabolism Characteristics of OCs

Compound	Phase I Metabolism	Phase II Metabolism
Ethinyl estradiol	CYP3A4 (major), CYP2C9 (minor)	SULT1E1 (major) UGT1A1 (minor)
Drospirenone	CYP3A4 (?)	
Norgestimate (Pro-drug)	CYP3A4	
Norelgestromin (17-deacetyl norgestimate)	CYP3A4	Glucuronidation & sulfation
Levonorgestrel	CYP3A4	
Desogestrel (Pro-drug)	CYP2C9, CYP2C19	
3-ketodesogestrel	CYP3A4	
Norethindrone	CYP3A4, 2C19	
Gestodene	CYP3A4	Glucuronidation

Pathways relevant for OC as a victim drug: CYP3A4/ UGT1A1 /CYP2C19/2C9

Sex Hormone Binding Globulin (SHBG) and its effect on OCs

- **Progestins binds to low capacity, high affinity receptors on SHBG**



- Impact of SHBG elevation on free drug concentration of progestins has not been well studied
- Progestin total exposure correlates with SHBG levels (Norethindrone, Levonorgestrel, 3-ketodesogestrel and gestodene)
- Time-dependent progestin PK for total AUC due to EE-mediated SHBG induction
- Multiple dose OC can be considered for DDI studies involving SHBG bound progestins
- The single dose PK study design can be considered for low SHBG binding progestin

PD Measurements in OC DDI Studies

Is PD characterization needed for OC DDI studies?

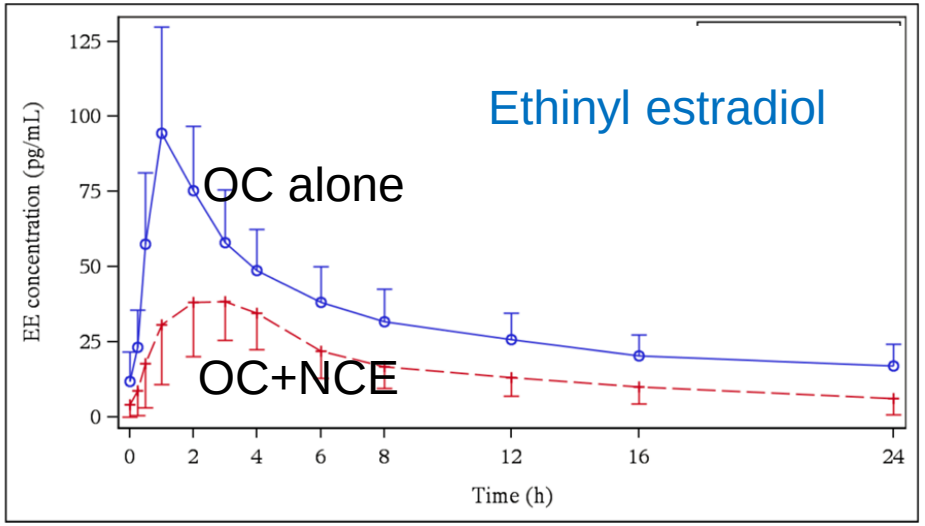
- **When to include PD measurement in the OC interaction study?**

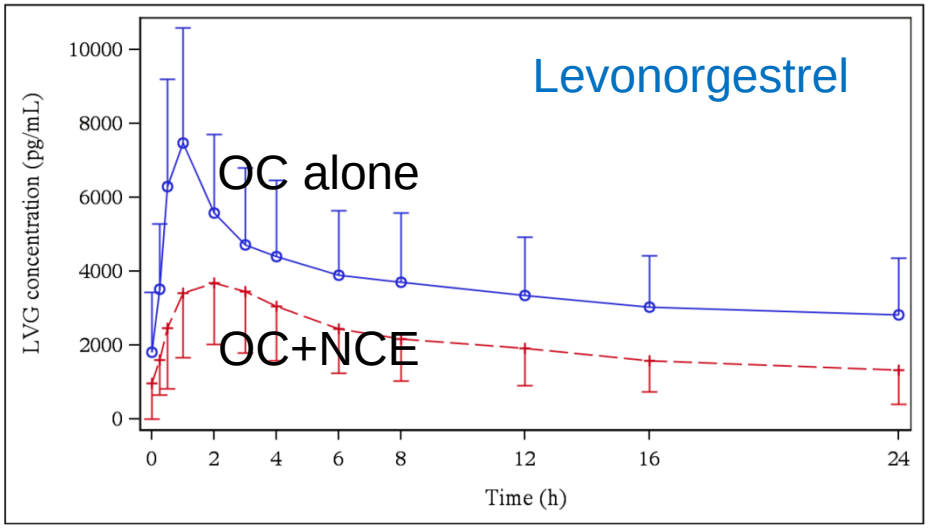
PD information may be helpful in some scenarios:

- NCE has relevant PD interaction mechanism that may alter hormone levels (eg: drugs for reproductive conditions, CNS drugs that may alter hormone production)
- PD endpoints serve as supportive information of maintained efficacy in spite of observed PK changes (however, published studies rarely have power to be definitive)

Case study with PK/PD component

- NCE is an oral agent for the treatment of Cystic Fibrosis
- EE 30ug/ LVG150 ug
- Single sequence, two-treatment period study (21days/period)
- Synchronized for 3 OC cycles if not already on OC
- In healthy premenopausal female volunteers
- Powered based on PK variability (n= 45 enrolled)





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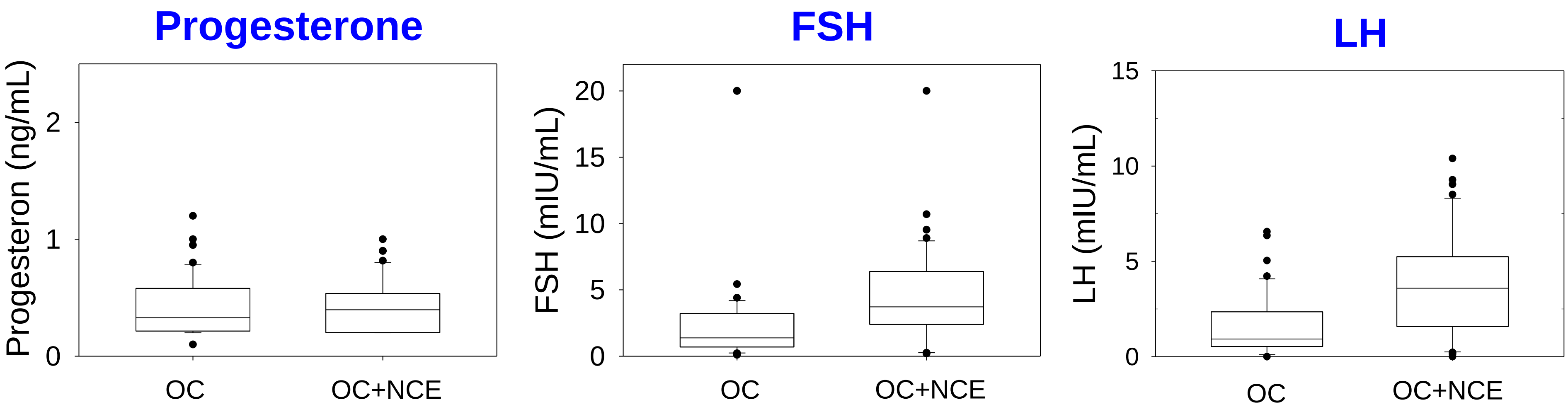
Pharmacodynamic measurements



PD parameters Median (range)	OC	OC+NCE
Estradiol (pg/mL):	20 (20-73.4)	23.5 (20-98)
Follicle size (mm):	5.40 (3.8 -18.1)	6.30 (0.0 - 23.0)
Hoogland score (score=4)	1 (1)	1 (2)

Progesterone level remains < 2ng/mL
Higher levels seen in mid cycle FSH/LH levels, minimal changes in other PD endpoints
Study concluded based on PK findings

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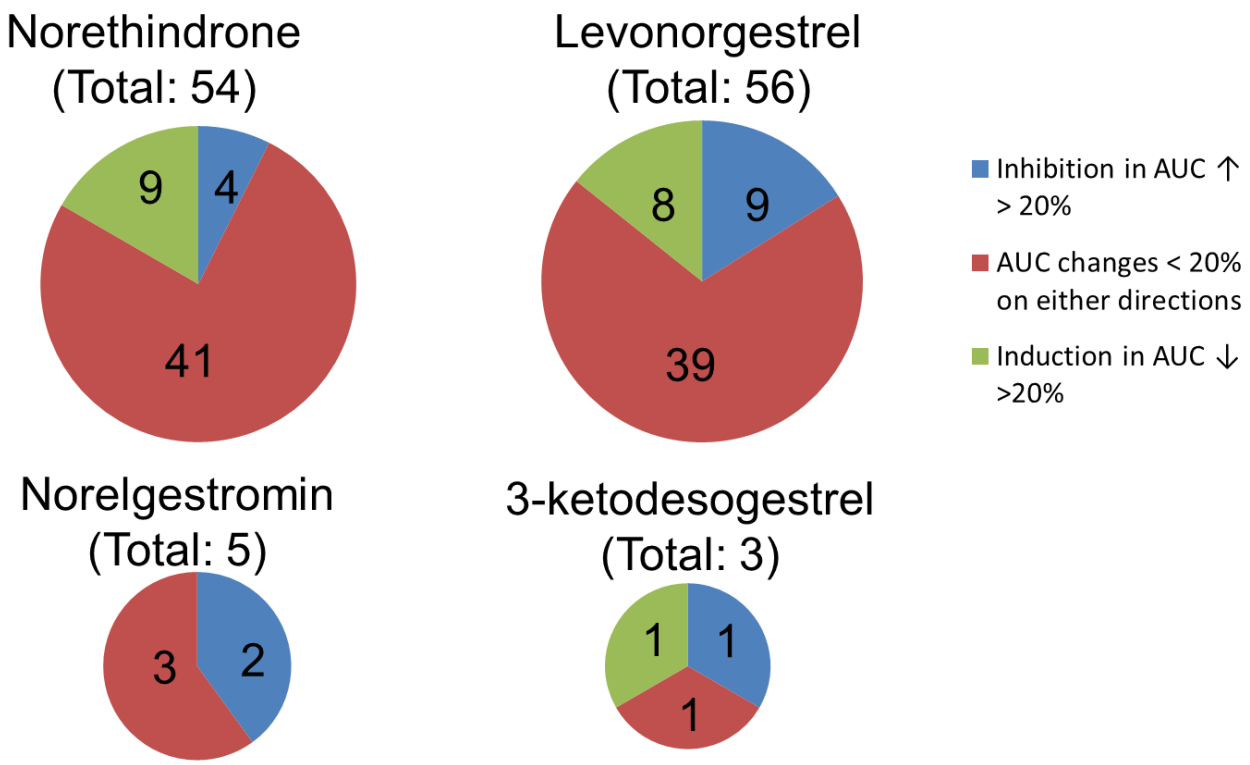
Challenges of PD data interpretation

- PK data drives the conclusions when interpreting OC DDI outcome
- For PD data as an endpoint to be included, convincing PD criteria need to be established for meaningful results interpretation
  - Determination of occurrence of ovulation is a composite assessment
  - PD endpoints and sampling points vary among studies
  - Clinical interpretation of data may differ amongst investigators

Clinical OC DDI

A summary of NCE impact on Progestin*



- Norethindrone and Levonogestrel are well studied
- Most of the studies showed clinical PK DDI < 20% changes

**** University of Washington, Drug interaction database program***

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Progestin exposure increase due to inhibition

	Inhibition increase in AUC>20%	Comments
Norethindrone	Voriconazole: 49%↑ Protease inhibitor: 50%↑most	**No effect:** known strong CYP3A4 inhibitor Boceprevir
Levonorgestrel	Faldaprevir: 44% ↑most Netupitant and palonosetron: 41%↑	
Norelgestromin (Norgestimate active metabolite)	Elvitegravir/cobicistat/ Emtricitabine/tenofovir: 126%↑ Lopinavir and ritonavir: 83%↑	
3-ketodesogestrel (Desogestrel active metabolite)	Itraconazole: 72%↑	**No effect:** Fluconazole

- PK changes do not always correlate with CYP3A4 inhibition; Change is generally small
- Inhibitors affect multiple enzymes: eg voriconazole
- Newer progestin drospirenone (Spironolactone analog): 2.5-fold change by ketoconazole reported

Progestin exposure decrease due to induction

	Norethindrone	Levonorgestrel	Norelgestromin	3-ketodesogestrel
Carbamazepine 600 mg daily	↓ 57%	↓46%		
Efavirenz 600 mg daily		↓59%	↓64%	
St John's Wort 300 mg bid			↓(11%)*	↓42%

- Limited comparisons suggest extent of induction by CYP3A4 inducers are qualitatively comparable (i.e. similar trend)
- Another OC study may be necessary if unexpected result is seen (as compared to *in vitro* or other *in vivo* results)

**In the study, oral midazolam clearance only increased by 52% by this St John's wort ext*

Review of Labeling Information

- Labeling information & literature reports of DDI studies for drugs commonly known to be inducers or inhibitors of COCs were reviewed (eg: antiepileptics, antivirals and antibiotics). Trends are captured below.

What type of study was conducted? (PK or PK/PD; single or multiple dose)

•No consistent pattern for types of studies (PK or PK/PD, SD or MD) regardless of their inhibition/induction potential

What information is used in the label? (PK data, PK/PD data or general text about inhibition/induction potential of NCE)?

• Inclusion of PD data rare but exists in the DDI section (eg: felbamate)
• Older drugs: Inhibition/induction potential of NCE mentioned, without any data
• Newer drugs: PK information included

Label Information & Literature Reports

Does the recommendation (use of additional contraceptive methods) differ based on magnitude of observed induction or the pregnancy category of the drug?

• Drugs in pregnancy categories 'C' & 'D' (US labels) include a recommendation to use additional methods of contraception, irrespective of the magnitude of interaction
• Drugs in pregnancy category 'X' include a recommendation for alternate methods of contraception

Summary

- The need for multiple dose OC PK measurement depends on PK characteristics including SHBG binding;
- Single and multiple dose PK-only studies are recommended as default in view of challenges associated with PD data interpretation;
- OC DDI extrapolation considerations
  - Lack of significant inhibition interactions on the progestin component, especially for those well studied progestins
  - Shared CYP3A4 pathways and the observed effect of 3A4 induction
  - A understanding of NCE inhibition/induction profile

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