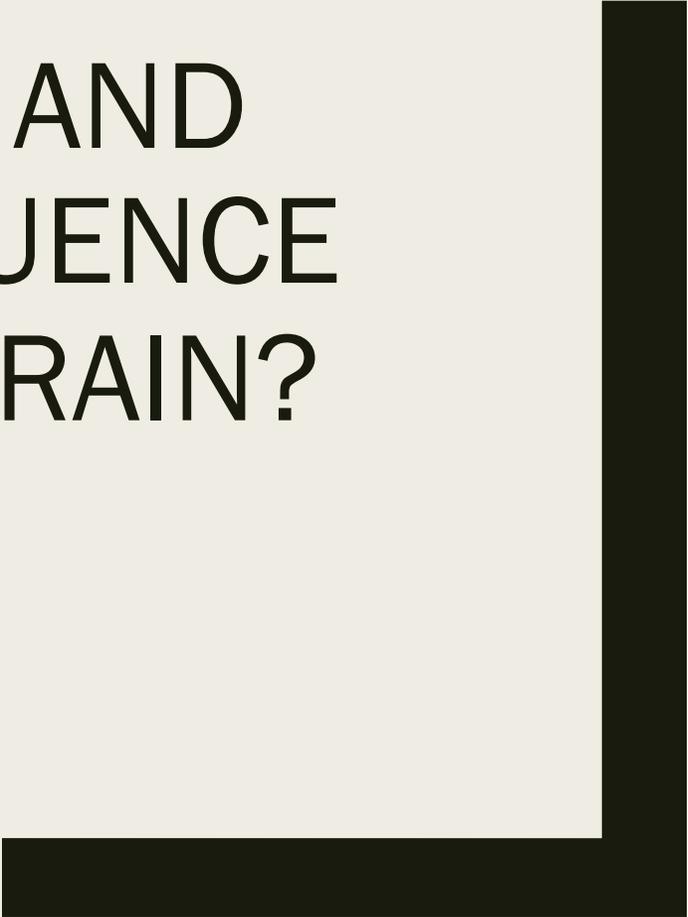
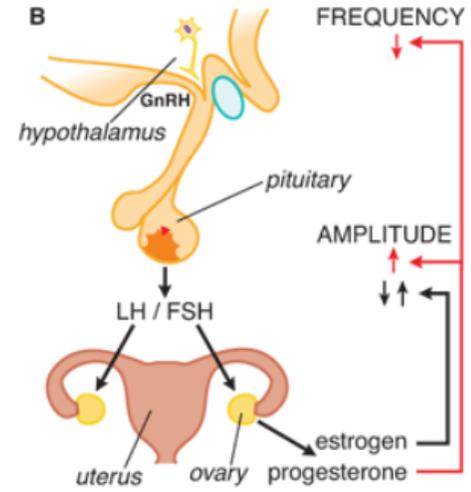
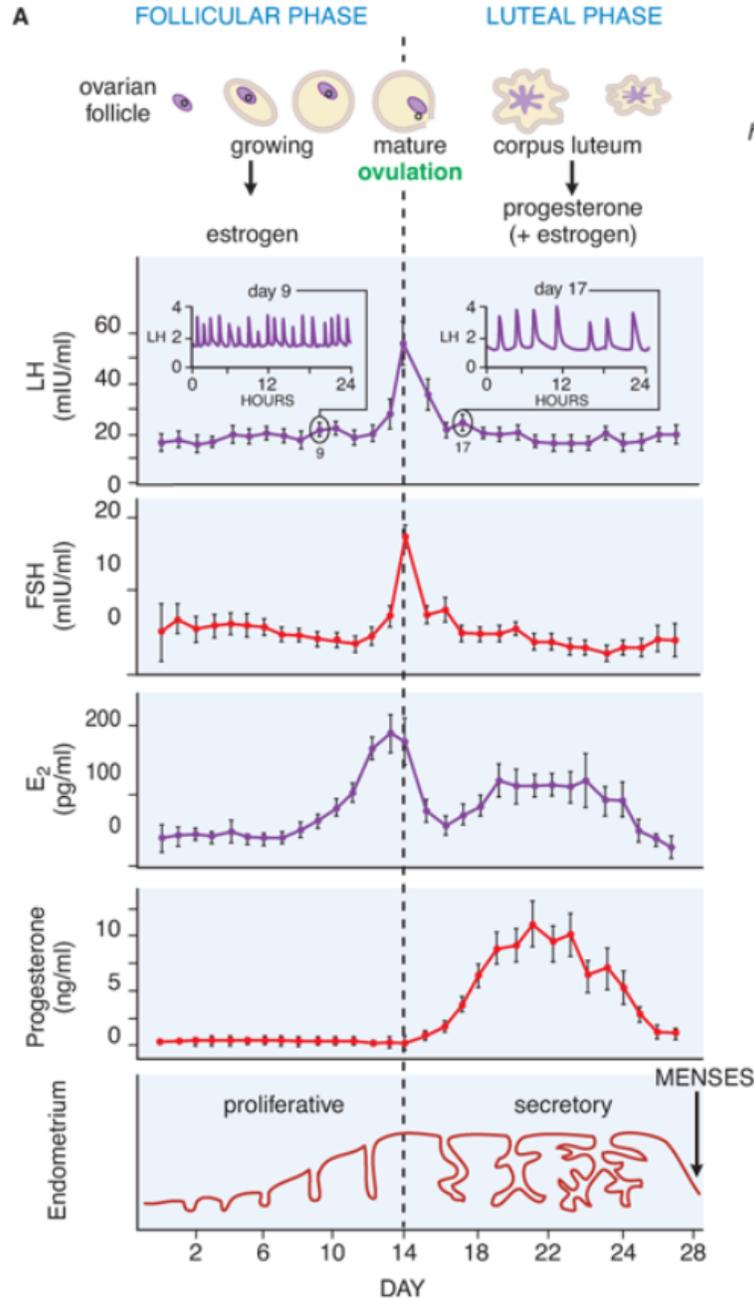


HOW DO ESTROGEN AND PROGESTERONE INFLUENCE BEHAVIOR AND THE BRAIN?

Pamela Derickson, MS-3

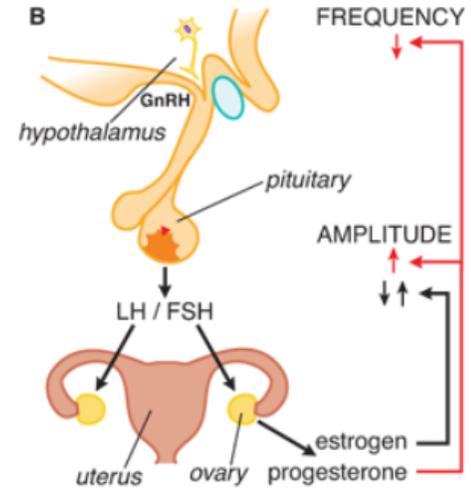
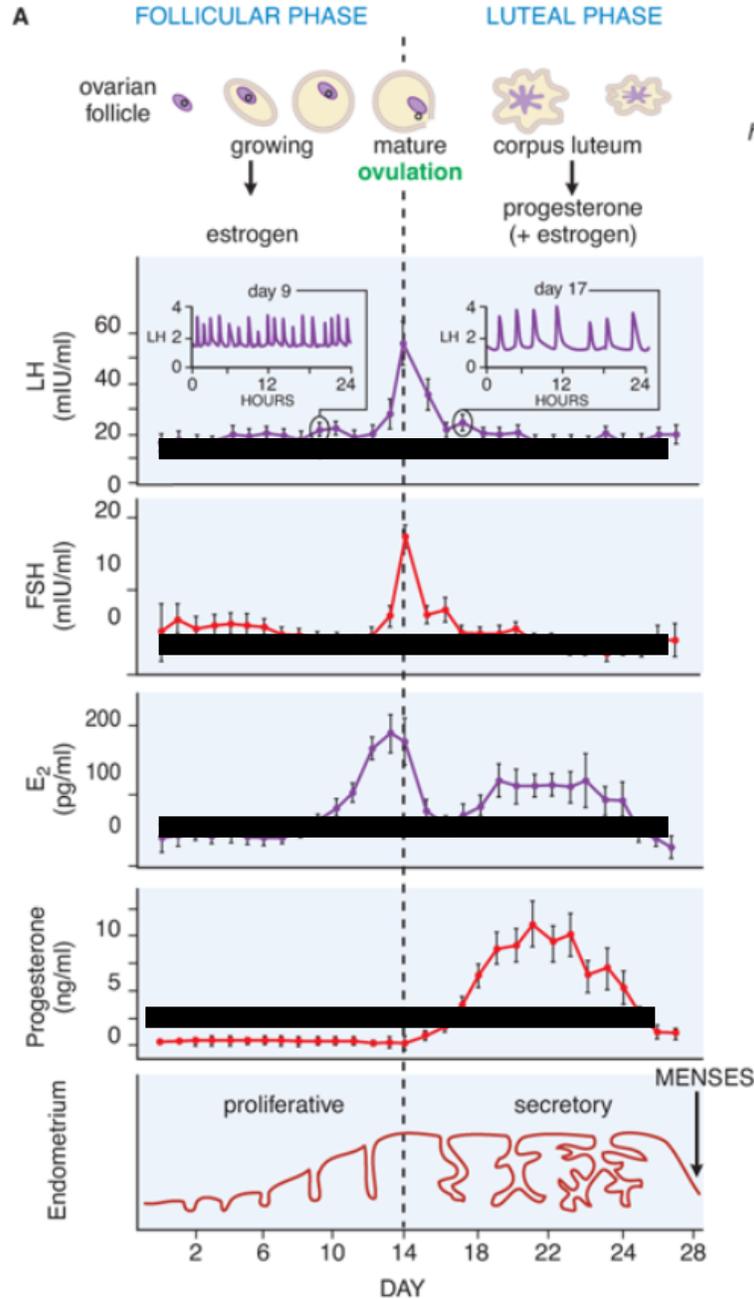




Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed. www.accesspharmacy.com
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Neuroendocrine Effects of Estrogen and Progesterone

- Estrogen has been shown to upregulate dopamine and serotonin receptors (Chavez, 2010)
- Progesterone levels have been linked to premenstrual dysphoric disorder, confusion, fatigue, and reduced confidence (Klatzkin, 2006)



Statistics about Oral Contraceptives

- Over 100 million women worldwide use the pill
- ~82% of sexually active women in the USA use oral contraceptive pills at some time during their reproductive years
- 17% of women in the US ages 15-44 currently use OCPs

How do OCPs work in general compared to natural states of hormonal secretions?

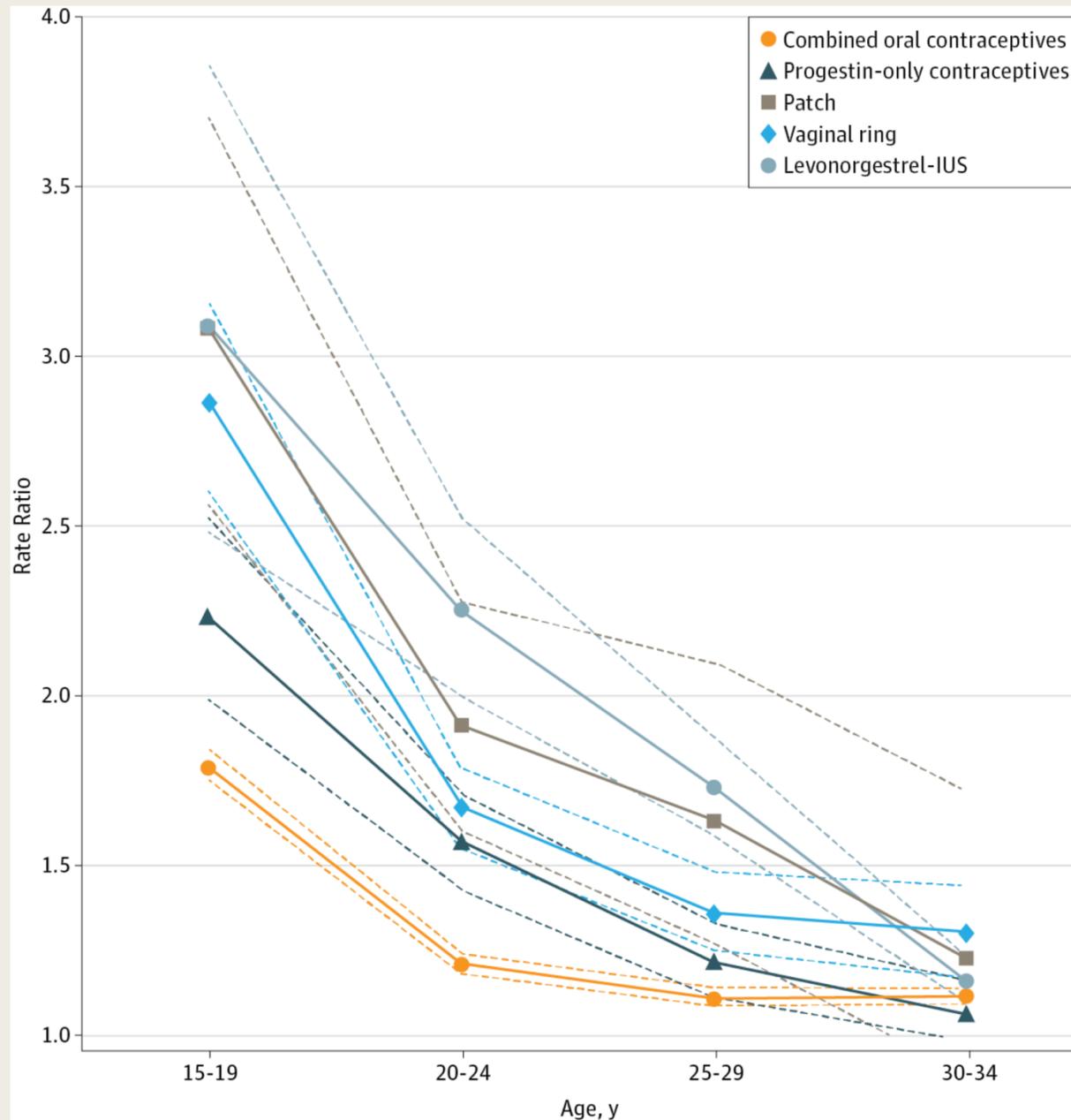
- Hormonal levels
 - OCPs have much smaller levels of estrogen and progesterone compared to a woman's natural cycle
 - Levels of progesterone > estrogen in OCPs
- Mode of secretion
 - OCPs reach steady state concentrations and inhibit GnRH, leading to lower serum concentrations of the hormones and fewer rapid shifts of the hormones



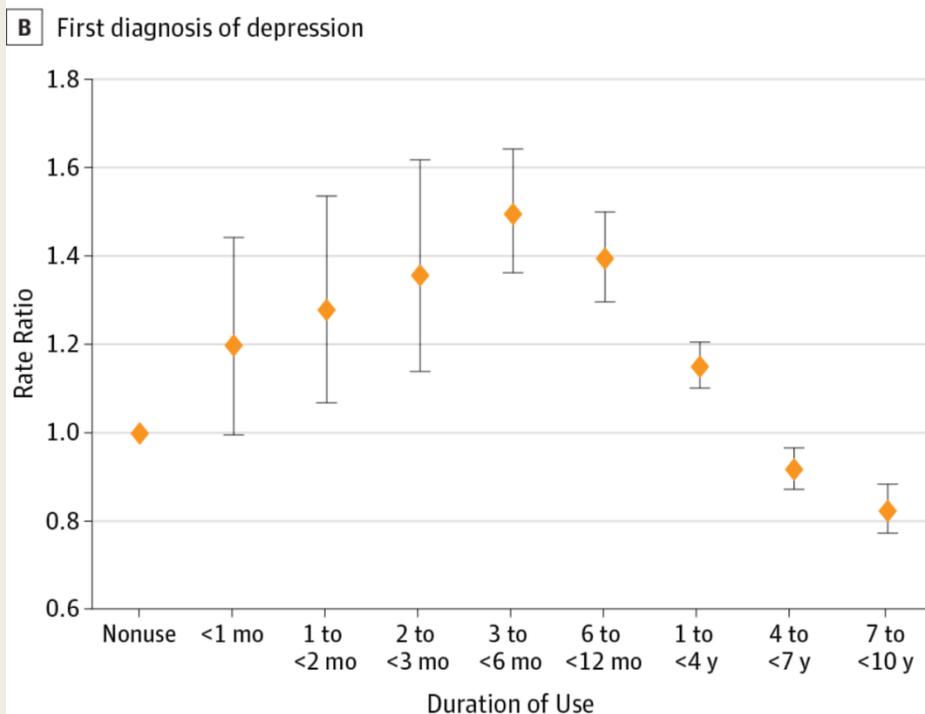
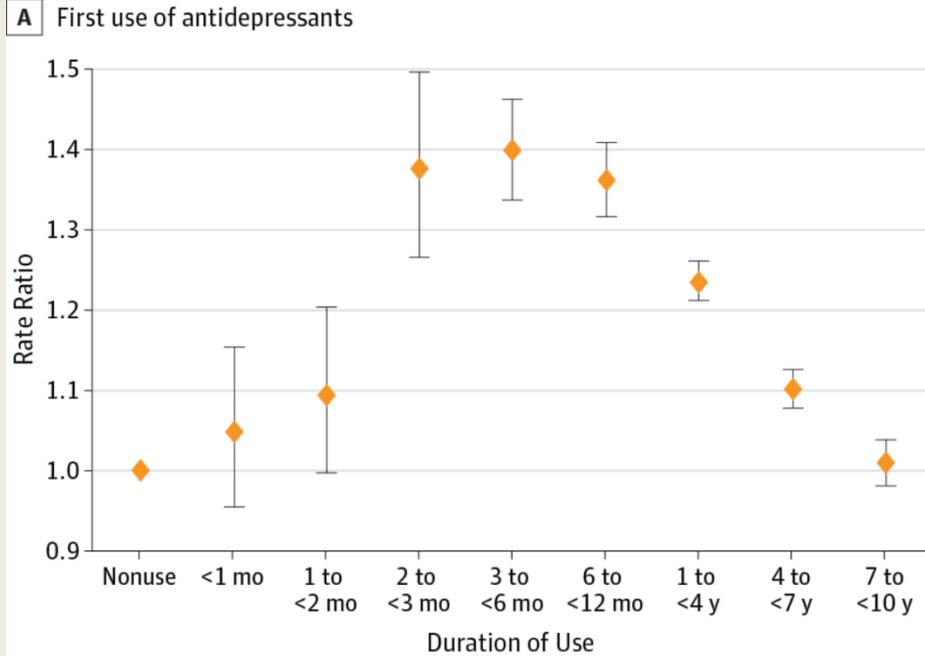
DO HORMONAL
CONTRACEPTIVES
INCREASE A WOMAN'S RISK
OF DEPRESSION?

Skovlund, et al. (2016) - *Association of Hormonal Contraception With Depression*

- 1.1 million women from a national registry in Denmark were followed for an average of 6.4 years between 2000 - 2013
 - Women with any prior psychiatric history were excluded from the study
- Greatest difference was in women ages 15-19:
 - Combined hormonal contraceptive group had a RR of 1.7 of first incidence of depression diagnosed in a psychiatric hospital
 - Combined hormonal contraceptive group had a RR of 1.8 of first incidence of using an antidepressant
 - The progestin-only pill group age 15-19 had a 2.2 risk of first time antidepressant and 1.9 first diagnosis of depression in a psychiatric hospital
- Risk increased at 2 months after initiation of hormonal contraceptive use, peaked at 6 months and after one year decreased significantly



- Figure 1, Skovlund, et al. 2016
- Rate Ratio of First Use of Antidepressants by Contraceptive Type
- Includes all women in Denmark aged 15 to 34 years
- Use of most types of hormonal contraceptives is compared with nonuse by participant age



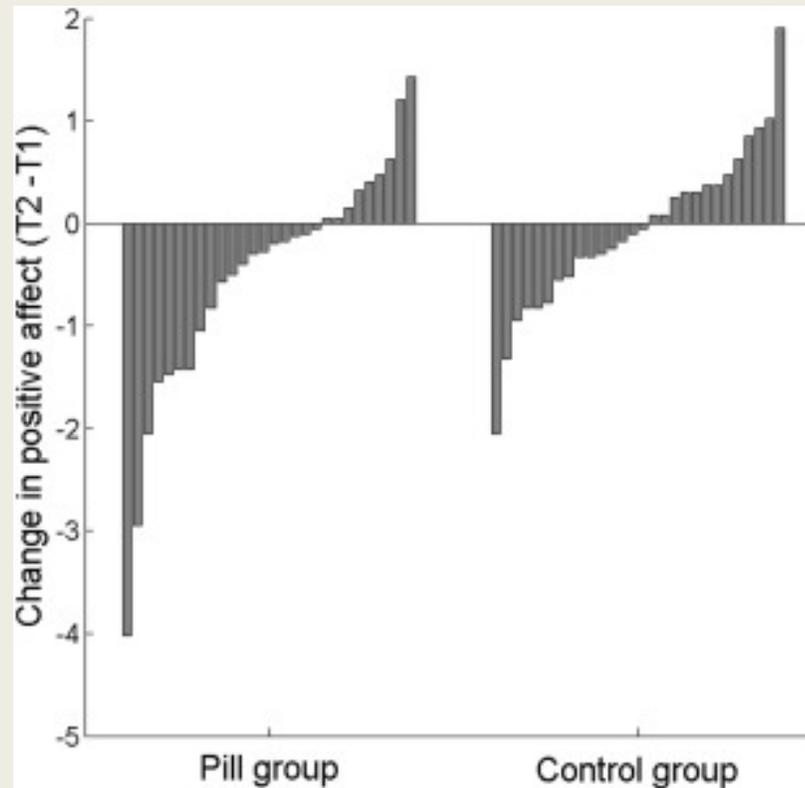
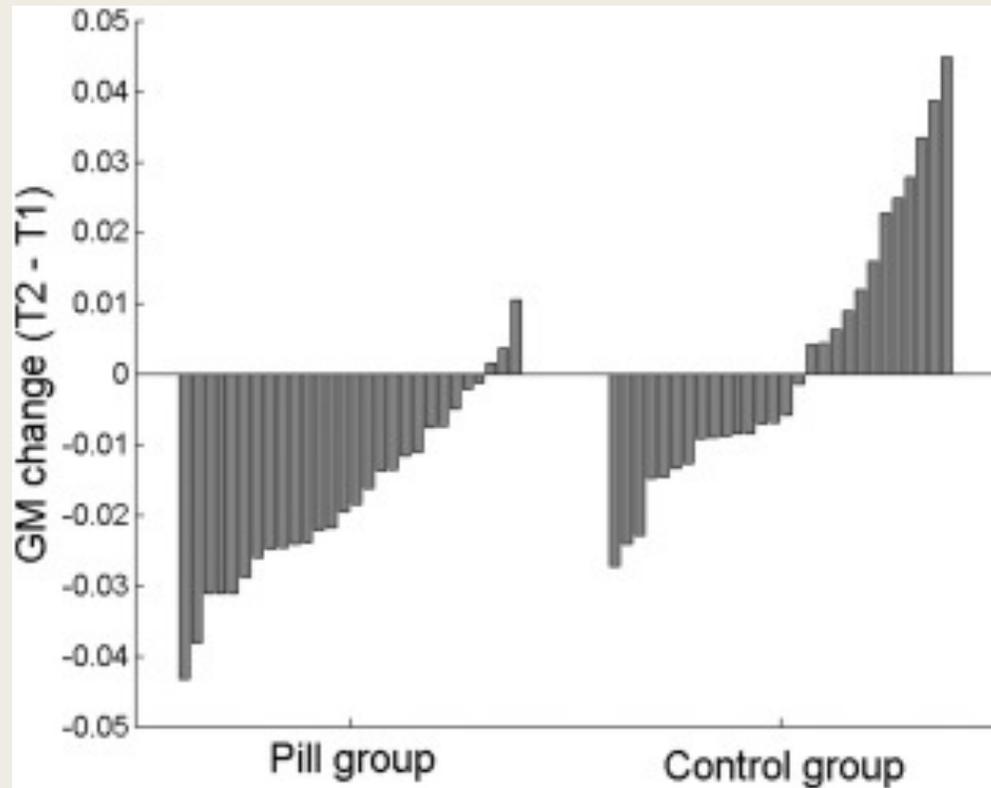
- Figure 2, Skovlund, et al. 2016
- Rate Ratios of First Use of Antidepressants and First Diagnosis of Depression
- Rate ratios are stratified by length of hormonal contraceptive use
- Error bars indicate 95% CIs.

Anderl, 2017

- Examined long-term associations between adolescent OCP use and mental health in adulthood
- Analyzed data from all women included in two large epidemiological datasets, the United States National Health and Nutrition Examination Survey (NHANES) and the National Longitudinal Study of Adolescent to Adult Health (Add Health)
 - Study involved 1,236 women, ages 20-39
- Across both datasets, OCP use during adolescence (independent of current OCP use) was associated with an increased likelihood (1.7X risk) of showing subclinical or clinical levels of depression and/or anxiety in adulthood compared to women who never used OCPs and who were started on OCPs after adolescence

Lisofsky, 2016 - *Hormonal contraceptive use is associated with neural and affective changes in healthy young women*

- Study investigated epigenetic changes after initiation of OCPs using neuroimaging techniques with the goal of investigating neural change in women using contraceptives
- Study participants were women, ages 16 to 35. Compared young women before and after 3 months of OCPs (n = 28), compared to naturally cycling women of comparable age (n = 28)
- The women on contraceptives had decreased gray matter volume in the left amygdala/anterior parahippocampal gyrus compared to the control group
 - Analysis revealed that gray matter volume in the left amygdala/anterior parahippocampal gyrus was associated with positive affect



- Figures 2, 5 from Lisofsky, et al. 2016
- LEFT: Individual change scores for gray matter (GM) volume in the amygdala and anterior parahippocampal gyrus between OCP and control group. Negative values represent a decrease in GM volume and positive values an increase in GM volume.
- RIGHT: Individual change scores for positive affect. Negative values represent a decrease and positive values an increase in positive affect.

Other psychobiological effects of estrogen and progesterone

- Hormonal contraceptives have been related to a decrease in the ability to have fear extinction (Wegerer, 2014)
- A single dose of estrogen in one study increased men's empathy (increased physiological response to another's pain, increased emotional reactivity) (Olsson, 2016)
- Women during ovulation had preference to more masculine faces, those on OCs did not have change in preference during the cycle (Penton-Voak, 1999)
- Highest sexual satisfaction in women was found in those who either met their partner when not on OC and did not get on an OC or those who met their partner on an OC and continued on an OC (Roberts, 2014)

Positive effects of OCPs

- OCPs in can cause improved quality of life by different means, including:
 - *Controlling a woman's ability to (not) get pregnant*
 - *Acne*
 - *Hirsutism*
 - *Heavy periods*
 - *Maintaining bone density*
 - *Decreased risk of certain cancers*
 - *Premenstrual dysphoric disorder*

Conclusions and Future Research

- There are clear benefits to using oral contraceptives in women of childbearing age to protect against unwanted pregnancies and other medical conditions
- The benefits of OCPs must be weighed with possible side effects of mood changes in women:
 - *Correlation between mood and hormonal contraceptive use (Skovlund, 2016; Lisofsky, 2016), specifically progesterone (Kleiber, 1996)*
- Many have suggested avoiding hormonal contraceptives in adolescence, as the brain and HPA axis are still developing (Skovlund, 2016; Anderl, 2017)
- More studies with more robust study designs to further correlate relationships between OCPs, mood, and neuroanatomic changes

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Joe Rogan Experience #968 - Kelly Brogan

<https://www.youtube.com/watch?v=cunSB69gaec>

