Female Reproductive Life Cycle and Hormones: Methodology to Improve Clinical Trials

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Women and Clinical Trials

In clinical trials, there are 2 competing ethical priorities regarding the participation of women. One is that women of childbearing potential could become pregnant during a trial, raising concern over fetal exposure to an agent of unknown reproductive safety. The other is the need for development of treatments specific to subpopulations of patients in order to better inform care. The US Food and Drug Administration (FDA) has advised in accordance with both of these important aims. Women have historically been excluded to varying degrees from participating in studies of new treatments, although in more recent years they have been allowed to participate to a greater extent under specific parameters. The FDA Center for Drug Evaluation and Research (CDER) Guidance for Industry specified that women of childbearing potential are to be excluded from the earliest phases of studies of new treatments.[1] In later stages of clinical trials, in order for women of childbearing potential to be included, informed consent about the lack of reproductive safety data must be provided, negative pregnancy test results must be obtained prior to receipt by the subject of the investigational drug, and participants need to be advised about acceptable methods of contraception. In some cases, the requirement of "double protection" contraception has been added to the protocol.

The FDA has also issued guidelines regarding gender studies in product development.[2] These guidelines support the need for analyses to assess gender differences with regard to drug efficacy and safety. However, the ability to conduct such analyses has been limited by the quality and amount of data that have been collected, as well as by the relative lack of power of such analyses. In addition, the policies of the National Institutes of Health support the inclusion of women in research. With few exceptions, women must be included in clinical trials, with specified enrollment and recruiting plans, and research proposals are required to include analyses for gender differences in phase 3 clinical trials.[3,4] Despite these initiatives, the impact on treatment has been limited.

In a quest to make medical decisions more personalized and maximally inform patient care, a more rigorous, systematic approach is required to realize the potential of analyses based on gender. There are important relationships between endogenous and exogenous reproductive hormones and the course and treatment of mood disorders that have yet to be fully understood. It would be a tremendous advance to better understand the psychopathology and treatment of psychiatric disorders such as major depressive disorder (MDD) in specific subgroups of women and to be able to tailor treatments accordingly. Our objective is to promote the systematic collection of female reproductive status and hormonal variables that may impact outcomes and allow for secondary analyses in central nervous system clinical trials. We will focus, in particular, on the relevance of such data for MDD.

The Female Reproductive Life Cycle, Hormones, and Mood

Major depressive disorder is more prevalent among women compared to men, and the differences are most prominent during the reproductive years.[5–7] Women represent the majority of those seeking treatment for MDD and entering trials for MDD. Periods of hormonal variability, such as the luteal phase of the menstrual cycle, the postpartum period, and the menopausal transition, represent times when a substantial subset of women experience mood disturbances.[8–12] Normal shifts in endogenous reproductive hormone levels can contribute to pathologic mood episodes in women, and one can hypothesize that MDD might in fact represent a highly heterogeneous disorder that can be better characterized among subsets of women and in comparison to men.

It is already established that exogenous treatment with female reproductive hormones can impact mood. For example, oral contraceptive pills are a first-line therapy for premenstrual dysphoric disorder, and estradiol is an effective treatment for some women with mood symptoms associated with the menopausal transition.[13,14] Similarly, mood disturbances that are associated with fluctuations in female reproductive hormones are also treated with serotonergic antidepressants, demonstrating that standard treatments for MDD may impact hormonally associated mood worsening.[15,16] Yet, investigators recently reported no difference in treatment outcome on the basis of menopausal status or the use of hormonal therapies among women treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression study.[17]

Despite compelling evidence that reproductive hormones are important in the expression of MDD, the story appears

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complicated. The biological underpinnings of the effects of reproductive steroids on mood are complex. For example, estradiol is known to impact the expression of genes involved in the transcription of serotonin receptors and the serotonin transporter protein.[18–20] Estradiol also influences dendritic branching and synaptic formation and pruning.[21–23] We have yet to adequately comprehend the clinical relevance of synergies or interactions between female reproductive hormones, neurotransmitters, and antidepressants, although animal models suggest important relationships.[24–28]

PROPOSAL FOR METHODOLOGICAL ADVANCEMENT

Methods

We propose that the elucidation of gender differences, the effects of endogenous hormones, and the use of exogenous hormones can be both facilitated and expedited by the following:

1. The use of a standard brief questionnaire implemented systematically at baseline in clinical trials for MDD to assess reproductive life cycle status and the use of exogenous hormones.
2. The addition to protocols of prospective menstrual cycle tracking (in applicable women), in consideration of the high prevalence of premenstrual mood exacerbation.
3. The use of additional modules that can be added to studies on a case-by-case basis for more in-depth study of reproductive history and the impact of reproductive life cycle transitions.

Feasibility

In clinical trials, women are routinely assessed for childbearing potential and must typically be using an approved method of contraception to participate. As the ascertainment of childbearing potential and documentation of contraceptive use are already taking place in clinical trials, a low-burden but systematic documentation of reproductive status and hormonal variables is an intuitive extension. Usually, collection of information is routinely carried out at the screening visit to assess the appropriateness of women of childbearing potential and the use of adequate contraception; however, documentation of specific variables such as menopausal status and the use of contraceptive hormones and hormone replacement therapy is usually not rigorous or systematic. Methodical inquiry and documentation about reproductive status and the use of hormonal therapies would require a minimal investment of time and resources but would represent a valuable opportunity to advance women's mental health and yield personalized medical approaches to MDD treatment. Investigators and sponsors may be able to identify strategies for the treatment of MDD and predictors of response status that would not otherwise be known.

Approach

The instrument we have developed, the Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire, can be found online at mgh-ctni.org/innovations/frlhq/. Module I is a brief questionnaire aimed at standardizing the minimal collection of relevant information about reproductive hormones and status. We have tried to minimize clinician burden by arranging questionnaires into modules, so that modules II–V can be utilized on a case-by-case basis when more detail is deemed to be warranted. Only module I is designed to be completed by the research clinician; modules II–V are completed by the patient.

In addition to use in clinical trials, these modules are also designed to be useful for health care providers in clinical practice.

Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire Modules

I. Childbearing potential, menopausal status, and menstrual cycle
II. Current use of hormonal therapies
III. Menstrual cycle tracking
IV. Hot flash diaries
V. Reproductive history and mood

Should Premenstrual Mood Exacerbation Be Factored Into Clinical Trials for MDD?

Of all of the discussed factors related to endogenous and exogenous reproductive hormones, the one that is most likely to complicate data interpretation and study outcomes in a trial for MDD is premenstrual mood exacerbation. The majority of women with MDD experience worsening of depressive symptoms in the luteal phase of the menstrual cycle.[29] Baseline and endpoint assessments of mood may be confounded by premenstrual mood exacerbation, with potential impact on study results. It is plausible that luteal phase worsening could complicate the interpretation of primary outcome data in MDD trials if it is not included in statistical modeling, even in randomized trials. Since collecting information about menstrual cycle phases and the use of hormonal contraceptive treatments that impact mood and treatment outcomes is not costly, such data collection is a practical and reasonable strategy to develop statistical approaches that account for premenstrual mood exacerbation in MDD trials.

CONCLUSIONS

It is conceivable, if not probable, that carefully conducted studies of the impact of endogenous and exogenous reproductive hormones on the course of treatment of MDD will inform the care of women with MDD. The collection of such variables in a way that is cost effective and of low burden will facilitate exploratory analyses within studies and the pooling of data across studies. In addition, prospective tracking of menstrual cycles across the duration of studies will allow for premenstrual mood exacerbation to be assessed as a variable that may affect outcomes during the trial.

Now may be an opportune time to introduce these new data elements as a best practice in registration trials, as the CDER at FDA established in 2010 a Data Standards Program

to identify and prioritize data standards for clinical trials.[30] A major goal of the Data Standards effort is to facilitate efficient and effective review of sponsor submissions by CDER. As part of the process, CDER in 2011 identified a set of therapeutic areas that could benefit from identification of indication-specific data elements,[31] and MDD was identified as one of these therapeutic areas.[32] Because FDA plans to seek outside advice on what MDD-specific variables might be routinely collected in MDD trials, this is an ideal time to discuss routine collection of the types of data elements suggested above to characterize endogenous and exogenous hormone status of women participating in these trials, so that routine collection of these data elements will be expected in all future MDD registration trials.

Drug names: citalopram (Celexa and others).

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