

## Executive Summary

# Biological, Behavioral and Physiological Consequences of Drug-Induced Pregnancy Termination at First-Trimester Human Equivalent in an Animal Model

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### Background:

Approximately 20% of all pregnancies in the U.S. end in abortion. The health implications of abortion on women continues to be a source of heated debate. Various health concerns have been reported, short- and long-term. These include both physiological (e.g. increased risk of cancer) and psychological effects (e.g. increased risk of mood disorders (including depression), anxiety, substance abuse, and suicide) on women who have undergone an abortion.

Given the seriousness of the potential mental health and physical consequences, and the difficulty of treating them if they occur, it is necessary to appropriately investigate these potential links to the abortion procedure. Unlike many other situations in medicine, there has not been any objective pre-clinical investigation of the potential serious physiological consequences of the termination of a viable pregnancy. Given the complex changes in the body associated with pregnancy, it is difficult to expect that terminating a viable pregnancy is without consequences.

### Goals and Experimental Design:

While there are clear differences between animals and humans, there are many similarities in the physiology, neurology, neurophysiology and the resulting behaviors (e.g. in stress). Animal models provide the scientist with a comparative approach to address various questions (e.g. depression, schizophrenia, etc.), at various levels (e.g. behavioral, neurophysiological, molecular, etc.), in a significantly more controlled environment, independently of potential social, moral and other influences. Rat models are used routinely in investigating the mechanisms and testing the efficacy of various drugs (e.g. antidepressants, antipsychotics, etc.) and are considered as a standard pre-clinical model for psychiatric disorders and drug testing. Thus, the goal of our study was to provide a pre-clinical investigation of the potential biological, physiological, and behavioral consequences of induced abortion in an animal model (a laboratory rat).

Our work sought to create a valid animal model in order to examine the impact of treatments known to induce the pharmacological termination of pregnancy relative to sham treatments in rats. Given that medical abortions in humans are performed up to the first 10 weeks of pregnancy, the pregnancy termination for this study was performed at mid-term (days 12–14) of the rat's gestational period (~23 days). This compares to days 28–40 (4–6 weeks) in human embryonic development. Our model utilizes parameters, considered in neuropsychology to be standard indicators of the physiological and behavioral changes associated with depression and anxiety-like behavior and stress. The specific parameters utilized within our study include:

- **Rat body weight and food intake** – as a measure of the general health and well-being of the animal
- **Vaginal impedance** – as a measure of fertility and indicative of estrus (period of sexual receptivity, similar to ovulation in humans)

- **Sucrose consumption** – a decrease of which is indicative of anhedonia (the loss of interest or pleasure; related to the diagnostic criteria for depression)
- **Locomotor activity** – as a measure of exploratory behavior: rearings (when the rat stands on hind legs), distance travelled, percentage time active, and overall speed during testing – related to the criterion of reduced physical movement in the diagnosis of depression
- **Corner activity** – as a measure of potential anxiety-like behavior (i.e. more time spent in corner of testing cage indicative of anxiety-like behavior)
- **Home-cage activity** – as a measure of general activity and related to reduced physical movement in depression
- **Forced swim test** – used as a measure of behavioral despair – standard test for testing antidepressant efficacy, though absence of abnormalities in the forced swim test do not rule out despair nor indicate degree of despair.
- **Oxidative balance measures** – used as biochemical markers of oxidative stress; altered in situations of physiological stress.

Given the role of animal models in assisting in our understanding of the biobehavioral mechanisms underlying human brain function and behavior, we propose that the findings from our study provide insight into the potential consequences of abortion in humans.

## Results:

Our findings indicate that pregnancy termination in a rat at first-trimester human equivalent using mifepristone and misoprostol induces:

- A **reduction in overall well-being**, as indicated by the significant reduction in **body weight** and **food intake**
- A significant reduction in the amplitude of the **vaginal impedance** peaks, reflective of an absence of the potential protective effects of carrying a pregnancy to full-term and delivering, on fertility/fecundity (the ability to reproduce)
- A potential stress-induced **anhedonic** effect (reflective of depression-like behavior) that is:
  - Comparative to moderate to severe stress, as reported in other studies
  - Reflected in the significant reduction in **sucrose consumption** during *Treatment Week* (week of pregnancy termination) relative to *Pre-Treatment Week*
  - Not related to the effects of the drug given that **sucrose consumption** during *Treatment Week* was significantly lower in the abortion group (pregnant rats that received the drug) relative to non-pregnant rats that also received the drug
- Other symptoms indicative of significant stress/depression and anxiety-like behavior associated with a **reduction in general mobility**, as indicated by:
  - Significant decreases in the various parameters measured of **locomotor behavior (distance, percentage time active, overall speed, rearing)**
  - A significant change in the amount of **time spent** in the back **corner** of the cage during behavioral testing, corroborating home-cage observations
  - A significant reduction in overall **home-cage activity** in rats
- Differences in **oxidative balance** that are distinct from the effects of pregnancy or drug administration alone
- Significant **differences from natural miscarriage** in **body weight** and **food intake**
- No significant changes in the forced swim test. However, ambiguous results have been reported in the literature, indicating depressant, antidepressant and no effects of stress on the forced swim test.

## **Conclusion:**

Thus, the findings of this study appear to indicate that drug-induced pregnancy termination at mid-term (first-trimester human equivalent) in the rat induces significant negative biological and behavioral effects, as well as long-term physiological changes.

To our knowledge, our study is the first report addressing the potential biological, behavioral and biochemical effects associated with pregnancy termination in an animal model. Additionally, the findings of this study also appear to provide additional support to the current literature pertaining to the benefits of carrying a pregnancy to full-term. Our findings strongly suggest that pregnancy termination at mid-term (first-trimester human equivalent) induces significant negative biological and behavioral changes in the rat. Additionally, such a procedure appears to be associated with a potential absence of beneficial effects of carrying a pregnancy to full-term. Moreover, our findings also appear to indicate a significant difference between induced pregnancy termination (medical abortion) and natural miscarriage. Our study, therefore, indicates the importance and necessity for further objective research into the abortion procedure, including at the physiological and neurophysiological levels. Such work may further our understanding and potentially shed some clarity into the potential biobehavioral impact of such a procedure at the level of the human person.

## **Future Direction:**

Future research will investigate:

- The potential reversal of the negative behaviors observed in this study following pregnancy termination,
- The neurophysiological mechanisms underlying the behavioral changes reported above following pregnancy termination
- Behaviors (e.g. drug addiction, maternal care of future litters, future pregnancies) that could be influenced by the potentially altered neurophysiological dynamics resulting from the procedure.