Stress and its influence on fertility in various organisms and how human physiology can be modeled in wolf spiders

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Honors Thesis

Abstract:

Every environment is filled with stressors that affect every organism that lives there. Different types of stress include predation, dietary, climate, and even social stress. Each species experiences a unique set of potential stressors, but they all create comparable results. Oocyte quality decreases with stress, be it heat stress in rabbits or psychological stress in mice. Humans are not exempt from stressors either, especially psychological or social stress. Women who experience high levels of stress in life can lead to fertility issues. One way to combat these issues is with in vitro fertilization (IVF). IVF success can be negatively influenced by the presence of stress both during the process and throughout the patient's life. Wolf spiders also experience psychological stress and seeing how it affects their ability to reproduce can help to understand how human stress functions. For female wolf spiders, adding dietary stress can decrease ovarian function and fertility. There are significant parallels between human and wolf spider responses to stress. Although the reproduction process of wolf spiders is not identical to humans, there are similarities and could prove to be a novel model for identifying behavioral and physiological patterns affected by stress.

Introduction:

On a general basis, stress refers to any event or circumstance that has a negative effect on the overall quality of an individual's life (Ebbsen et al. 2009). All organisms experience stress. Animals like rabbits and mice are constantly aware of the dangers of predation. Humans undergo similar types of stress daily, as well as relationship induced stress, workplace stress, and other unpleasant life events. Stress impacts an organism on the physiological level, often decreasing fitness (Ebbesen et al. 2009)). The main goal of this paper is to show how stress in females can

negatively affect reproductive success. Fecundity, ovulation time, and number of oocytes produced tend to be negatively impacted in humans when exposed to stress. It can also decrease the likelihood of conceiving (Ebbesen et al. 2009). Although many studies address this connection, some hypotheses cannot be tested on humans because they are invasive or unethical. This paper will also address how studies use other organisms as models for human reproductive physiology, and why it is important to have these models. We will focus on how gathering information on animal stress helps predict what types of stress can affect humans. Lastly, we will discuss how wolf spiders can be an important model in this connection with humans.

Humans:

Humans often experience social stress, either through their own personal relationships or events that occur in their life. Humans experience stress. The stressors can take on many different forms like environmental, psychosocial, and dietary. One study (Bleil et al. 2012) suggests that the presence of stress might cause an acceleration in reproductive aging. Environmental adversity is thought to promote earlier fertility by increasing the number of follicles that grow in a female, which may cause the female to experience early onset menopause because of depletion of the ovaries. This happens because the body evaluates the risks of waiting to mature given the stressful situation and begins increasing follicle growth to ensure the female has time to reproduce. For this study stress was measured through a questionnaire regarding the individuals general life. Reproductive aging was measured through a follicle count and analyzed with many factors including age and stress level. The results imply that women experiencing greater stress will become fertile faster and experience higher antral follicle count loss as they age. The results of this study demonstrate that the rate of follicle loss is higher in women who experience more psychological stress. It is difficult to compare stress in a population, especially

when the method is self-reporting and the questionnaire only asks to report on situations in the past month. Also, confounding factors like parity, the presence of smoking, and BMI were not analyzed in this study. However, reported feelings of stress have been seen as a drawback in the overall reproductive health of women.

High levels of stress in life can become a problem if one aims to conceive. Experiencing stress has previously been linked to a decrease in conception rate (Ebbesen et al. 2009). In fact, merely conceiving can be a stressful event. It is possible that stress surrounding the process of in vitro fertilization (IVF) plays a negative role in the success of the treatment. A study by An et al. (2012) evaluates whether psychological stress, changes in the hypothalamus-pituitary-adrenal (HPA) axis, and if changes in the sympathetic nervous system influences the reproductive outcome of someone going through (IVF). Psychological stress is often correlated with HPA dysregulation and potentially an increase in the sympathetic nervous system (An et al. 2012). Different levels of cortisol and epinephrine have been identified as potential factors in the successfulness of IVF, and were measured at four different time points in duration of the treatment for this study: before the start of treatment, the day of oocyte retrieval, the day of pregnancy detection, and at 5-8 weeks of gestation for the patients that become pregnant (An et al. 2012). The study by An et al. (2012) showed that the norepinephrine and cortisol levels were significantly lower on the day of oocyte retrieval in the group that became pregnant. There was also a connection between lower levels of cortisol at the time of the pregnancy test and positive results. There was even a significant association between state anxiety and live birth rate. High levels of stress in pregnant females are important because it can cause several complications including spontaneous abortion and preterm delivery (Orr et al. 2002). A potential mechanism is

that significant stress could inflame the uterine lining and affect the production of progesterone (An et al. 2012).

Stress in humans appears to play an important role in the success of conceiving, but it is crucial to recognize other possible factors that play a role in reproductive success. It has been hypothesized that the diet of a female can influence the possibility of maintaining a pregnancy (Ladipo 2000). When a woman is pregnant, there is an increased need for various micronutrients to ensure healthy development of the fetus. Deficiencies in iron can cause anemia and has been connected with maternal mortality. If a woman's diet is deficient in iodine, there is a possibility of many complications including fetal loss and mental impairment in the newborn. In addition, pregnant women require about 20% more vitamin A because blood vitamin A concentrations tend to decline in pregnancy because of hemodilution (Ladipo 2000). Folic acid is also an important aspect of a pregnant woman's diet that can reduce birth defects. Another study indicated that the implication of micronutrient rich snacks into the diet daily before conception reduced the likelihood of gestational diabetes (Sahariah et al. 2016). This data indicates the importance of a nutrient rich diet for pregnant women. It also emphasizes how the presence of dietary stress can cause developmental issues in the fetus. Women in developing countries are more likely to experience these deficiencies, if they do not regularly have a well-balanced diet. A lack of essential nutrients can have a negative effect on the overall well-being of the offspring.

Other Animals:

To further study the effects of stress on female reproduction it is important to use other animal models. These model organisms help us understand how different stressors in controlled environments can affect reproduction and elucidate potential mechanisms behind these reproductive effects.

Rabbits:

Homeotherms, like mammals, typically expend a lot of energy to maintain their normal body temperature (Gordon 2012). Temperatures outside of "normal" values can cause increased stress. This is important because with global climate change the average temperature is supposed to rise significantly in the next generation, which could affect human reproductive rates. New Zealand White Rabbits, *Oryctolagus cuniculus,* were investigated by Mutwedu et. al (2021) for heat sensitivity to predict the possible effects of climate change on reproductive rates. New Zealand White Rabbits are sensitive to heat stress, and it has been shown to decrease many factors including blood platelet count, red blood cell count, and even litter size and weight. It is hypothesized that these rabbits have issues eliminating body heat when it becomes excessive (Marai et al. 2002). Exposure to extreme heat was shown to have drastic changes on the organism in general, especially on the relative weight of each organ (Mutwedi et al. 2021). High temperatures also impact the quality of oocytes, specifically in telophase I and metaphase II (Mutwedi et al. 2021). Other studies have shown that the rate of conception and milk yield in rabbits is also reduced at high temperatures (Marai et al. 2002). This study is important to show that changes in an environment can drastically decrease the overall fitness in an individual because it can cause organ weight, including reproductive organs, to decrease along with a decrease in oocyte quality. It would be unethical to replicate this study in humans because the rabbits had to be euthanized to dissect their organs. It would also be dangerous to place a woman under this much heat stress, but we can take these results and model them towards the likely physiological response in humans.

Mice

Mice are a classic model organism evaluated in research since its findings can be related to human physiology. There are several studies regarding the idea that stress has a negative impact on reproductive success in mice (Kala and Nivsarkar 2016), but the specific mechanism of psychosocial stress on ovulation of mice is less explored. Targeting superoxide dismutase (SOD) is a potential indicator on the pathway of how this phenomenon works (Kala and Nivsarkar 2016). SOD is an enzyme that converts a superoxide radical to oxygen and hydrogen peroxide in all cells in the body (Abreu and Cabelli 2010). This catalyst is involved in ovulation, as luteinizing hormone induces SOD to create hydrogen peroxide so it can begin the formation of progesterone. One study evaluates several different factors including cortisol level, behavior, estrogen cycling, follicular growth, and the quality and quantity of the oocytes that are produced (Kala and Nivsarkar 2016). All the mice experienced five different types of stressors in this study: restraint, slanted cage, dirty bedding, isolation, and no bedding in their cage. Cortisol levels were identified and found that there was an increase in the experimental group. The mice also began to develop depression, anxiety, and anhedonia which is an inability to feel pleasure typically associated with depression. Emotional factors are crucial to the overall health of an organism, so it is unsurprising that the female mice also experienced a delay in ovulation when compared to the control group. After the completion of the treatment, the histology of the mice was studied, and it was found that there was an increase in the number of atretic antral follicles and a decrease in corpora lutea. Antral follicles are important because they have the oocytes that are needed for fertilization, they create and secrete the hormones that are needed for estrous cyclicity. Antral follicles are also important in maintaining the reproductive tract, so a decrease in these follicles can negatively influence ovulation and ovulatory functions. There was increased expression of SOD1 in all stages in the estrous cycle in the experimental group, which

may create anovulation and infertility. Overall, the mice that experienced the stressful treatment produced a lower number of oocytes supporting the concept that psychological stress can alter the reproductive functions in any organism, including humans.

Spiders

Similarly to the other organisms evaluated in this paper, spiders experience various types of stress including psychological and environmental stress, which can directly contribute to their mating success. Wolf spiders, in the family *Lycosidae*, have several studies regarding stress and its effect on mating. These studies in particular have the potential to help contribute to our understanding of human reproduction as they could have unique contributions not often utilized. One way we can use spiders to study the effects of stress on reproduction is by varying the diet to see its effect on reproductive outcomes.

A species of Wolf spider, *Pardosa pseudoannulata* preys on the fruit fly *Drosophila melanogaster* and can extract certain macronutrients from them as they feed (Feng et al. 2022). The quantity and quality of macronutrients in a prey has been thought to directly affect the spider's growth and reproduction. The study observed this phenomenon by using two different groups of fruit flies with different lipid content, and then feeding them to two groups of female spiders until they reached maturation. Once the spiders were mature mating behavior, sexual cannibalism, reproductive success, and offspring quality were analyzed with the spider's lipid content. This study demonstrated that the lipid content of a female does not influence their mating behaviors, but it did positively aid their fecundity. Females with a high lipid diet laid more eggs than those who were fed a low lipid diet. This study shows the importance of a quality diet in wolf spiders, which is similar to how a nutrient-filled diet is an important part of human fertility and maintaining a successful pregnancy (Ladipo 2000).

What happens when you have a balanced diet, but it is tainted with a toxin? In industrialized countries the soil can become polluted with various metals such as cadmium (Cd) (Wang et al. 2020). Cd is a toxic metal that can be spread up the food web as it is absorbed into plants and can undergo bioaccumulation through herbivores into carnivores. Wolf spiders, particularly *Pardosa psuedoannulata*, are common in agricultural fields in China and help to control pests. Wang et al. (2020) assessed the effects of Cd exposure and how it can affect reproductive function. This was achieved by feeding spiders fruit flies (*Drosophila melanogaster*) which have been treated with Cd. Ovarian tissue was dissected from spiders to identify detoxifying enzyme activity and eggs were harvested. The results showed that the activities of Glutathione S-transferase (GST), peroxidase (POD), and superoxide dismutase (SOD) were decreased when exposed to Cd. There was also a significant decrease in the number of eggs produced by the experimental group exposed to the toxin. It was identified that 24 genes were expressed differentially in the mitogen-activated protein kinase signaling pathway, which is a structure important in oocyte meiosis and maturation in the ovary. These findings show that exposure to a toxic metal like Cd can have many different negative effects in the female reproductive system, which can overall affect their fertility. This can be related to toxins finding their way into human diets, like how levels of mercury have been identified in fish (Freire et al. 2010). Prenatal exposure to mercury can have severe effects on cognitive development. The prevalence of this topic helps to show how the detoxifying enzyme activity that was recorded in the spiders can be related back to humans and how they might respond if they were exposed to a similar toxin.

Another environmental factor that has become an issue recently is the elevated level of carbon dioxide in the atmosphere. It is a potential cause of climate change, and it can negatively

affect both plants and animals. Zuo et al. (2015) investigates how this elevation in CO_2 levels can affect several different reproductive aspects of *Pardosa astrigera*. The wolf spiders were treated with varying amounts of carbon dioxide concentrations, and it was shown that spiders in a higher CO_2 environment experienced a delay in maturation. There was not a difference in the oviposition rate or hatching rate of eggs in the female spiders regardless of the amount of CO_2 they were given, which is good news. However, females in the high-CO_2 group produced less eggs total than the group in the low-CO_2 environment, indicating that high-CO_2 levels can decrease fecundity in *P. asterigera*. These studies show that placing a stressor on any organism's environment can negatively impact their overall fecundity and the quality of oocytes. This effect is potentially a result of organisms spending more energy towards surviving with less focus on reproducing.

Conclusion:

Experiencing stress can be impactful in many aspects of life. Reproduction and the behaviors surrounding it can be influenced by many different types of stressors. Changes in the environment of an organism can influence the quality of the eggs produced by females. Many aspects of climate change, including CO_2 elevation and temperature, can decrease overall reproductive success with decreases in maturation as well as overall organ atrophy (Mutwedi et al. 2021). These factors can also influence the number of eggs produced by a female (Zuo et al. 2015).

Dietary stress can also be an influential factor in the reproductive success of organisms. A proper diet with the appropriate micronutrients helps to provide a developing fetus with the proper building blocks so they can develop normally (Ladipo 2000). Sufficient nutrients in a diet is shown to be correlated with higher fecundity (Feng et al. 2022). Conversely, if a diet is

deficient in micronutrients or has toxins this can cause stress and interfere with reproductive potential (Wang et al. 2020). This trend is modeled in both humans and wolf spiders, showing how connections can be made about stress and fecundity through several organisms. It also shows how future studies can use wolf spiders to model human physiology. This is significant because experiments can use this connection to induce different types of dietary stressors onto wolf spiders. Through this type of experiment, their maturation, oocyte quality, and overall egg quantity can be measured. The results can be interpreted and modeled in how humans might react to the same treatment.

Evaluating the correlation between stress and fertility is important because both play a major role in everyday life. Most things in human life induce different types of stress and it is important to understand how each can impact oocytes, gamete quality, and overall likelihood of conception. Experimental studies often use other organisms such as mice in place of humans so they can more intensely manipulate variables and control the experiment. It is unethical to induce these types of stressors in humans, but we can relate the results found in other organisms to human physiology. It is important to gather information regarding fertility because many families struggle to conceive and understanding all the potential factors could increase their likelihood of success. Reproduction in wolf spiders could also be used as a model for humans because they have similar reproductive processes. The process is similar enough to relate the results towards human behavior and encourage future studies. Inducing stress on wolf spiders was found to overall decrease fecundity, like its effect on humans did. The different types of stress that can be induced in wolf spiders varies from what is ethical to induce in humans like inducing starvation, inducing psychological stress, and manipulating environmental variables. These factors often must be assessed using observational studies in humans. Assessing

reproductive behaviors and physiological responses to stress in spiders can lead to future studies that can also be related back to human behavior, which is essential in fully understanding the implications of stress in the likelihood of conceiving a pregnancy.

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