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Progesterone's effects on the psychology of disease avoidance: Support for the compensatory behavioral prophylaxis hypothesis

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ABSTRACT

In the human menstrual cycle, luteal phase immunomodulation prevents the maternal immune system from attacking the half-foreign blastocyst should conception occur, thereby facilitating implantation and development. However, tolerance of the conceptus comes at the cost of increased vulnerability to infection. The compensatory behavioral prophylaxis hypothesis (Fessler, 2001; Fessler & Navarrete, 2003) holds that evolved psychological mechanisms enhance avoidance of potential contaminants during periods of reproductive immunomodulation so as to decrease the likelihood of infection. Because such immunomodulation is triggered by progesterone, this hormone is predicted to correspondingly enhance behavioral prophylaxis and the motivational states underlying it. We investigated specific domains of disease avoidance psychology in a nonclinical sample of women ($n = 120$) by measuring salivary progesterone in naturally cycling women. We find that progesterone correlates directly with the degree to which women report emotions, thoughts, and behaviors consonant with enhanced prophylaxis.

Throughout human evolutionary history, women have experienced increased vulnerability to infection at regular intervals as a consequence of specific hormonal shifts. Physiological immune vulnerability can be counteracted through 1) recognizing cues of potential contagion and 2) avoiding or removing these cues through prophylactic behavior. Although prophylactic behavior can decrease disease transmission, such behavior entails the costs of increased time and energy devoted to disease avoidance and the loss of potentially valuable opportunities for social exchange. In light of these costs, the compensatory behavioral prophylaxis hypothesis holds that, rather than being constant, prophylactic behavior should be enhanced during periods of increased susceptibility to infection. Specifically, reactions to circumstances associated with the risk of pathogen transmission are predicted to vary in an adaptive manner, enhancing prophylactic behavior during times of elevated susceptibility. Because the hormone progesterone regulates the cascade of physiological events that culminates in increased vulnerability, progesterone can be expected to also mediate the psychological changes that elevate this compensatory prophylaxis.

The goal of the present investigation is to directly test the compensatory prophylaxis hypothesis using convergent and ecologically valid measures that assess sensitivity and aversion to cues that have recurrently been associated with infection.

The menstrual cycle involves patterned changes in immune responses that are necessary for pregnancy. Thus female reproductive endocrine functioning offers an opportunity to test the compensatory prophylaxis hypothesis as mediated by reproductive hormones. From an immunological perspective, pregnancy entails the problem that the maternal immune system, which normally detects and attacks foreign entities, must now tolerate the presence of paternal genetic material. This is achieved through a downregulation of inflammatory immune responses, a process ultimately controlled by progesterone.

Highly elevated during pregnancy, progesterone is also produced during the latter portion of the menstrual cycle in anticipation of pregnancy. The menstrual cycle consists of functionally distinct phases marked by characteristic variations in hormonal levels. The highest levels of progesterone outside of pregnancy occur during the luteal phase, the period after the rupture of the ovarian follicle during which the corpus luteum secretes progesterone (Hatcher and Namnoum, 2004). During the luteal phase, the body prepares for conception and implantation of the blastocyst by down-regulating inflammatory immune responses. Luteal phase immunomodulation is an adaptation that prevents the maternal immune system from attacking the half-foreign blastocyst, thereby facilitating implantation and development. A cost of such tolerance, however, is that women are more prone to infection during this phase (reviewed in Fessler, 2001).

The downregulation of inflammatory immune responses during the luteal phase is apparent in a variety of ways. Studies have shown levels of pro-inflammatory cytokines decline, and natural killer cells

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are downregulated (Bouman et al., 2001; Faas et al., 2000; Trzonkowski et al., 2001). Other studies have shown that relative to TH1 inflammatory immune response TH2 or anti-inflammatory immune response is increased luteally (Faas et al., 2000). Luteally, symptom severity declines in autoimmune diseases, such as rheumatoid arthritis, that are characterized by excess pro-inflammatory activity, while the converse is true of disorders, such as lupus erythematosus, that are characterized by excess anti-inflammatory activity; correspondingly, consistent with the important defensive functions of inflammation, response to vaccination is attenuated (Kozlowski et al., 2002) during this time, and chronic infections worsen (Wilder, 2006).

To date, only two studies have sought to directly test the effects of progesterone on compensatory prophylaxis. Fessler and Navarrete (2003) failed to find increases in prophylactic attitudes, as measured by self-reported disgust reactions to hypothetical situations, during the high-progesterone phase of the menstrual cycle. However, the interpretation of these results is constrained by the fact that, particularly as regards issues relevant to disease transmission, the instrument employed (see Haidt et al., 1994) relies on a variety of unusual questions, including some hypothetical situations that were likely viewed as outlandish by many participants. In contrast to this null result, in six studies, (Jones et al., 2005) found that women showed an elevated preference for healthy over unhealthy faces during periods of presumed or measured progesterone elevation. While clearly supporting the compensatory prophylaxis hypothesis, Jones et al.'s findings are limited in that social contact is only one avenue of potential pathogen transmission, yet this hypothesis predicts attitudinal and behavioral changes in many such avenues.

In addition to the aforementioned, a number of studies have examined the compensatory prophylaxis hypothesis indirectly. Fessler et al. (2005) found elevated disgust sensitivity, primarily in the food domain, in the first relative to the second and third trimesters of pregnancy, a period of heightened vulnerability to infection. Navarette et al. (2007) found the same pattern with regard to hostility toward outgroup members, individuals often conceptualized as sources of disease. Although meat, a principal source of foodborne illness, is frequently avoided during pregnancy (Fessler, 2002; Flaxman and Sherman, 2000) we failed to find a reduction in meat consumption during the high-progesterone phase of the menstrual cycle (Fleischman and Fessler, 2007). Lastly, Conway et al. (2007), who view progesterone's effects on behavior during the menstrual cycle as a byproduct of mechanisms designed to protect the fetus during pregnancy, found that, during the high-progesterone phase of the cycle, women perceive facial expressions of both disgust and fear as more intense when the faces display averted gaze compared with direct gaze; the authors posit that, compared to direct gaze, averted gaze is more indicative of the presence of a looming threat in the environment, as direct gaze implies that the viewer herself is the target of disgust or fear. While the increase in sensitivity to environmentally-elicited facial expressions of disgust is consistent with the compensatory prophylaxis hypothesis, the additional sensitivity to facial expressions of fear is not predicted by this perspective.

In keeping with the information above, our overarching prediction is as follows:

> because progesterone affects the immune system in ways which increase vulnerability to transmissible disease, increases in circulating progesterone levels will be accompanied by changes in psychology that, via concordant behavioral changes, can be expected to adaptively reduce the probability of infection during periods of increased susceptibility to pathogens.

The emotion disgust is thought to be universal in humans, and, correspondingly, is associated with a unique facial expression (Ekman and Friesen, 1986). Curtis et al. (2004) proposed that disgust evolved to bias humans away from sources of infection. If disgust is an adaptation that functions to protect humans from sources of disease, heightened disgust sensitivity should aid in further preventing disease. We therefore predict that disgust sensitivity will increase as progesterone, and thus vulnerability to disease, increases.

Obsessive–compulsive disorder (OCD) spans many adaptively relevant domains. For example, intrusive and obsessive thoughts about social appropriateness may be an overexpression of the need to manage reputation, while compulsively checking the security of oneself, one's home, and one's kin may be an overexpression of normal defense of self and inclusive fitness interests (Brune, 2006). Likewise, we suggest that one of the major domains of OCD, contamination obsessions and washing compulsions, is an overexpression of attitudes and behaviors that have adaptively reduced the probability of infection. Indeed, consonant with the immunological consequences of female reproductive hormones, researchers have found that this facet of OCD is more frequently expressed by women (Bogetto et al., 1999; Castle et al., 1995), and that OCD onset is likely to follow reproductively relevant events such as menarche and pregnancy (Labad et al., 2005). OCD symptoms are exacerbated premenstrually (Vulink et al., 2006; Williams and Koran, 1997). We interpret these observations as follows: because the contamination domain of OCD is directly disease-relevant, while other aspects (intrusive thoughts, checking behavior, and repetitive rituals that do not involve cleaning) are not, we expect that only changes in the former will reflect the influence of progesterone. Moreover, viewing the spectrum from healthy to clinical as a continuum, we expect to find subclinical increases in OCD-like thoughts and behaviors in normal individuals as a function of progesterone levels; consonant with this expectation, prior research indicates that healthy women engage in more unusual cleaning behavior in the luteal phase (Dillon and Brooks, 1992).

In modern societies, the public bathroom is a context in which people frequently encounter cues of contamination. Many sufferers of OCD struggle both with using public restrooms and the desire to engage in compulsive handwashing afterward (Abramowitz et al., 2008). We therefore expect that public bathroom behavior should offer an avenue for exploring subclinical OCD-like disease avoidance in a healthy population.

Women diagnosed with trichotillomania, the obsessive pulling of hair, increase this behavior during the luteal phase and early stages of pregnancy (Keuthen et al., 1997). We surmise that this may be due to an overexpression of the prophylactic behavior of grooming, removing parasites and preventing them from penetrating the body envelope. Because women are more vulnerable to infection during high progesterone periods, we hypothesize that women will be especially vigilant about what may be on the skin during this time period. Thus we predict that, during periods of high progesterone, women will have a lower threshold for experiencing the compulsion to remove from the body anything that gives off cues of the presence of ectoparasites.

Methods

Instruments

Disgust sensitivity instrument: Rating of Curtis images

Curtis et al. (2004) conducted an online study in which over 40,000 participants rated photographs depicting objects, people, or situations varying in their association with the threat of disease transmission, finding that people reported much greater disgust to stimuli linked to disease transmission. Employing the Curtis et al. photographs, we asked participants to indicate how disgusted they would feel were they to interact with the object, person, or situation in reality (e.g., “How would you feel about touching this?” etc.), with responses recorded on a Likert scale from 1 to 10 anchored by “not at all disgusted” and “very disgusted”.

Revised Padua OCD Inventory

The Revised Padua Obsessive–Compulsive Inventory is a self-report measure of chronic OCD symptoms that separates "worry" from compulsions and obsessions (Burns et al., 1996). We modified the inventory in order to investigate menstrual cycle phase-dependent OCD-like symptomology in normal women by adding the phrase "In the last 24 hours" to the beginning of each question. For conceptual purposes, we divide the Padua inventory into questions that are contamination-related (questions 1–10 and 39) and those that are non-contamination-related (all other questions). Examples of contamination-related questions include "In the last 24 hours I've felt my hands were dirty when I touched money," and "In the last 24 hours if I touched something I thought was 'contaminated,' I immediately had to wash or clean myself." Examples of non-contamination questions include "In the last 24 hours before going to sleep, I've had to do certain things in a certain order," and "In the last 24 hours when I heard about a disaster, I've thought it was somehow my fault."

Bathroom behavior scale

Employing interviews and focus groups composed of women demographically similar to our prospective participants, we compiled a list of behaviors that women engage in public restrooms that are subjectively motivated by disgust or feelings of contagion. Selecting seven of the most highly-endorsed items, we created a questionnaire examining behavior in public bathrooms. Examples of items include "In the last 24 hours, have you used a paper towel or anything else to open a bathroom door rather than touching it with your hands?" and "In the last 24 hours, have you washed your hands two or more times in the bathroom?". Each item was accompanied by a scale where participants could indicate their answer ("N/A", "no", "once or twice", or "a few times"). Because very few participants endorsed "a few times", the data were not sufficiently variable to afford principal components analysis. We therefore performed an item-total correlation, removing two items that did not correlate at the 0.40 level or above (Cronk, 2004). The final $r_s = 0.56$ on this measure indicates acceptable internal consistency (See Appendix A).

Ectoparasite removal/Grooming survey

In order to investigate grooming behaviors in healthy women that are potentially explicable as progesterone-mediated ectoparasite removal or exaggerations thereof, we developed a questionnaire with 13 items addressing behaviors such as skin picking, scratching, and picking at scabs ($\alpha = 0.73$). As orifices are one avenue whereby parasites can bypass the host's skin barrier, the questionnaire includes items addressing picking, scratching, or investigating orifices. Examples of items include "In the last 24 hours, have you picked at a scab?" and "In the last 24 hours, have you picked at or around your eyes?" (see Appendix B).

Participants

Participants were recruited from the Introduction to Psychology subject pool at the University of Texas at Austin. A total of 189 women completed the study. Criteria for exclusion included use of antidepressants ($n = 5$), use of antibiotics ($n = 1$), and use of amphetamines (e.g., Adderall, etc. — these medications tend to increase skin picking behavior and OCD symptomology (Koizumi, 1985) ($n = 3$). Women who were sick or in significant pain during the time of the survey, or who stated they had been sick or had an infection within a week before the survey, were also excluded ($n = 35$), as normal immune changes that occur as a result of progesterone could be disrupted by these phenomena.(Kiecolt-Glaser et al., 2002). Women who reported that physical symptoms were due to seasonal allergies were retained. Women who had invalid hormone assays were excluded ($n = 19$). This left 79 women who were naturally cycling. For each analysis we excluded women who did not complete the measure.

Procedure

Employing a cross-sectional design, we asked all participants to complete in a single sitting a computerized instrument composed of our modified version of the Revised Padua OCD Inventory, disgust ratings of the Curtis et al. visual stimuli, our bathroom behaviors survey, our grooming survey, and a general survey investigating medication use, health, and reproductive history, including menstrual cycle dates. Salivary samples were collected at the time of participation for subsequent hormonal assay. Participants were asked to salivate directly into a plastic pharmaceutical vial upon arrival to the laboratory before they had viewed any experimental stimuli. The vials were sealed and frozen at −20 °C until analysis. In addition to retrospective information on the participant's menstrual cycle, upon completion of the instruments, participants were given a stamped and addressed postcard and were asked to return it upon the onset of their next menstrual bleeding.

Hormone assay data

Progesterone was assayed by the first author using an enzyme linked immunosorbent assay (ELISA) kit purchased from Salimetrics (State College, PA, USA). The sensitivity of the assay, defined as lower limit of detection that can be distinguished from the zero standard, was 5 pg/mL. Mean inter- and intra-assay coefficient of variation for the participants retained for analysis were 14.00% and 3.60%, respectively.

Results

Scores on the Padua, the Bathroom behaviors scale and the Grooming scale were not normally distributed, and participants did not endorse the full range of values on each item (e.g., on a scale of 0–4 on the Padua inventory, fewer than 1% endorsed the highest value). Thus we used the nonparametric Spearman's Rho for these items. Salivary progesterone values were log-transformed for all analyses. Progesterone increases so dramatically during the luteal phase that log transformation is often used for analyses to correct for non-normal residuals.

Prediction 1. *Women will show a positive correlation between salivary progesterone and OCD symptomology in the domains of contamination and washing compulsions, but will not show a correlation with regard to symptomology in other domains of OCD.*

We found that contamination-related OCD symptomology ($r_s(79) = 0.31$, $p < 0.01$) was significantly correlated with log transformed salivary progesterone. There was a non-significant trend for non-contamination-related OCD symptomology to also correlate with progesterone ($r_s(79) = 0.22$, $p > 0.05$) (Fig. 1).

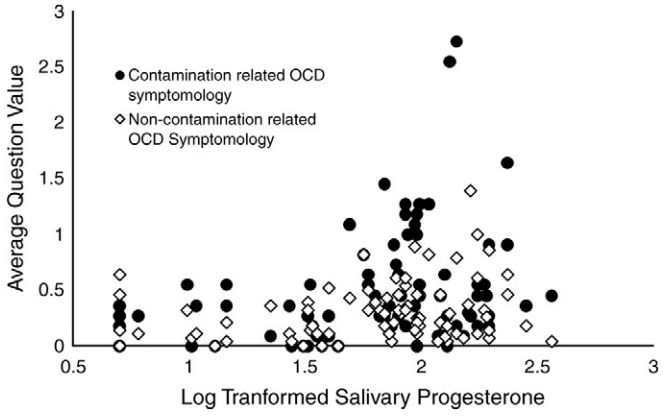

Fig. 1. Relationship between log transformed salivary progesterone and self-reported contamination related and non-contamination related OCD symptomology.

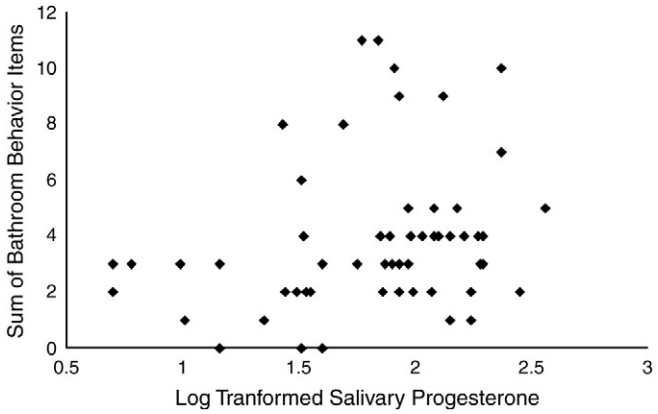

Fig. 2. Relationship between log transformed salivary progesterone and self-reported disease avoidant bathroom behaviors.

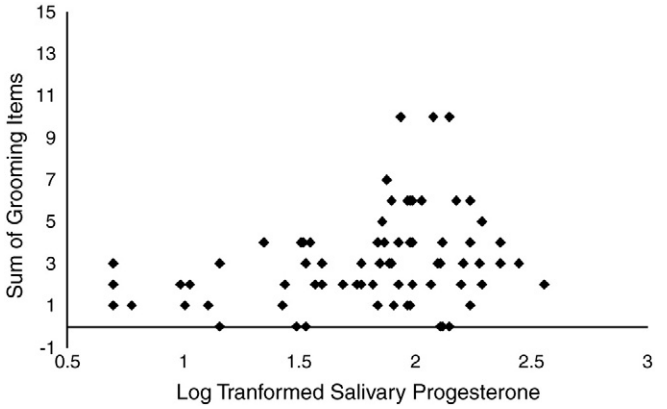

Fig. 4. Relationship between log transformed salivary progesterone and self reported grooming behavior.

Prediction 2. *Women will show a positive correlation between salivary progesterone and bathroom behaviors related to disease avoidance.*

We excluded women who had not used a public restroom in the last 24 h, leaving us with 56 naturally cycling women. Log transformed salivary progesterone correlated significantly with self-report of these behaviors (r_s (56) = 0.29, $p = 0.03$) (Fig. 2).

Prediction 3. *Women's salivary progesterone will correlate positively with disgust sensitivity.*

Log transformed salivary progesterone and disgust sensitivity were significantly correlated (r (79) = 0.25, $p = 0.02$) (Fig. 3).

Prediction 4. *Women will report engaging in more ectoparasite-linked grooming behaviors as progesterone increases.*

Excluding three women who did not complete the entire grooming survey, we were left with 76 naturally cycling women. Grooming behavior was significantly correlated with log transformed salivary progesterone (r_s (76) = 0.25, $p = 0.04$) (Fig. 4).

Discussion

Results from our cross-sectional study support the principal prediction derived from the compensatory prophylaxis hypothesis, namely elevations in self-reported disease-avoidance behaviors and attitudes as progesterone, the hormone responsible for reproductive immunomodulation, increases. Contamination-related obsessive–compulsive-like ruminations, disgust responses to photographs, and grooming behaviors plausibly linked to ectoparasite removal were all positively correlated with levels of salivary progesterone.

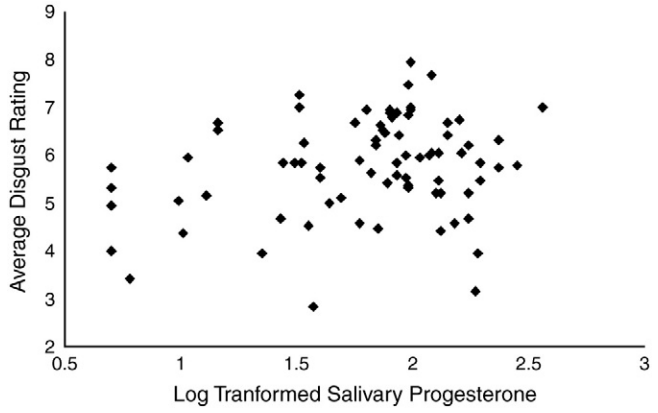

Fig. 3. Relationship between log transformed salivary progesterone and self reported disgust to photographic stimuli.

Ruminations unrelated to contamination were nearly correlated with salivary progesterone. The reason for this is unclear. Perhaps the cognitive readiness necessary for contamination related behavioral prophylaxis also causes intrusive cognitions and fearful ruminations. The anterior insular cortex, an area of the brain that responds preferentially to images of contamination and facial expressions of disgust (Wright et al., 2004 but see also Schienle et al., 2002) also responds to fear inducing images (Stark et al., 2003). Perhaps the fact that disgust and fear are built into the same neural system constrains the expression of one without the other. However the fact that only the contamination-related portion of the OCD inventory showed a significant correlation with progesterone, along with response to disgust eliciting images leads us to tentatively surmise that this is the central aspect of adaptive cognition at work.

This study has some limitations. The participants were surveyed in a cross-sectional fashion that could not reveal the degree to which individual women changed in their disease-avoidance behaviors as they progressed from a low to a high progesterone period. Additionally, survey measures may not accurately represent disease avoidance behaviors engaged in during daily life. Self-grooming behaviors in particular are unlikely to be well remembered as they usually occur without much conscious thought. Thus, future studies could naturalistically observe self-grooming behaviors or the grooming response of participants to stimuli linked to the presence of ectoparasites. Using a behavioral measure of women's interactions with actual objects and situations that provide cues of contamination would provide a more ecologically valid test of the predictions derived from the compensatory behavioral prophylaxis hypothesis.

This line of research has the potential to generate a number of clinical applications. For example, if subsequent investigations support the link between progesterone and OCD symptomology, women suffering from OCD may well benefit from therapies that lower their circulating levels of progesterone. Likewise, should our future investigations reveal differential effects for different types of exogenous progesterone-like substances, this may usefully inform clinicians' recommendations regarding hormonal contraceptives or hormone replacement therapy, particularly for patients with a history of OCD.

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Appendix A. Bathroom behaviors questionnaire

1. In the last 24 hours, have you washed your hands two or more times in the bathroom?
2. In the last 24 hours, have you used a paper towel or anything else to open a bathroom door rather than touching it with your hands?
3. In the last 24 hours, have you covered a public toilet seat with a toilet seat cover or toilet paper before sitting down?
4. In the last 24 hours, have you flushed a public toilet in any other way than with your bare hand (e.g. with your foot, with your hand covered)?
5. In the last 24 hours, have you wiped two times or more after urinating?

Appendix B. Self grooming questionnaire

All questions had a scale attached with "Not at all", "Once or twice", "A few times", "Several times" except for "In the past 24 hours have you felt unusually itchy?" which had the options "not at all", "somewhat", "very".

1. In the last 24 hours, have picked at or around your eyes?
2. In the last 24 hours, have you pulled at peeling skin on your body that was not a scab?
3. In the last 24 hours, have you picked at your mouth, gums, lips, or tongue?
4. In the last 24 hours, have you picked at a scab?
5. In the last 24 hours, have you used your finger to probe your ear canal?
6. In the last 24 hours, have you used a Q-tip or other object to clean out your ears?
7. In the last 24 hours, have you pulled off a piece of your toenails?
8. In the last 24 hours, have you picked your nose?
9. In the last 24 hours, have you pulled off pieces of skin from your feet, including the soles and calluses?
10. In the past 24 hours, have you scratched a part of your body until it was red?
11. In the past 24 hours have you felt unusually itchy?
12. In the last 24 hours, have you used your teeth to scratch an itch?
13. In the last 24 hours, have you picked in or around your vaginal area (not including pulling at hair)?

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