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Interaction of menstrual cycle phase and sexual activity predicts mucosal and systemic humoral immunity in healthy women

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HIGHLIGHTS

- Sexually active women had higher IgG at ovulation than sexually abstinent women.
- Women reporting high frequency of sexual activity had decreased IgA at ovulation.
- Women reporting low frequency or no sexual activity had increased IgA at ovulation.
- Condom use was associated with an increase in IgG at ovulation.

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ABSTRACT

Several studies have documented shifts in humoral immune parameters (e.g., immunoglobulins) across the menstrual cycle in healthy women. It is thought that these shifts may reflect dynamic balancing between reproduction and pathogen defense, as certain aspects of humoral immunity may disrupt conception and may be temporarily downregulated at ovulation. If so, one could expect maximal cycle-related shifts of humoral immunity in individuals invested in reproduction – that is, women who are currently sexually active – and less pronounced shifts in women who are not reproductively active (i.e., abstinent). We investigated the interaction of sexual activity, menstrual cycle phase, and humoral immunity in a sample of 32 healthy premenopausal women (15 sexually active, 17 abstinent). Participants provided saliva samples during their menses, follicular phase, ovulation (as indicated by urine test for LH surge), and luteal phase, from which IgA was assayed. Participants also provided blood samples at menses and ovulation, from which IgG was assayed. Sexually active participants provided records of their frequency of sexual activity as well as condom use. At ovulation, sexually active women had higher IgG than abstinent women ($d = 0.77$), with women reporting regular condom use showing larger effects ($d = 0.63$) than women reporting no condom use ($d = 0.11$). Frequency of sexual activity predicted changes in IgA (Cohen's $f^2 = 0.25$), with women reporting high frequency of sexual activity showing a *decrease* in IgA at ovulation, while women reporting low frequency or no sexual activity showing an *increase* in IgA at ovulation. Taken together, these findings support the hypothesis that shifts in humoral immunity across the menstrual cycle are associated with reproductive effort, and could contribute to the mechanisms by which women's physiology navigates tradeoffs between reproduction and immunity.

1. Introduction

Natural variations in adaptive immunity across the menstrual cycle are complex, yet critical for understanding determinants of women's health. Research characterizing these variations is inconsistent, with some studies documenting significant decline in lymphocytes such as B-cells around ovulation [1–6], while others show increases (e.g., [7]) or no significant change across the menstrual cycle (e.g., [8–10]). Menstrual cycle-related variations could reflect a dynamic balance between prioritizing reproduction and defense: reducing certain aspects of immunity around ovulation may reduce immune disruption of conception. If so, we would expect such shifts only in women who are reproductively active – that is, regularly engaging in sexual activity. Few studies of women's immune response report on sexual activity status; however, this variable may explain the inconsistencies observed across studies.

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In the present study, we examined the impact of sexual activity on variations in circulating immunoglobulins across the menstrual cycle.

Within the humoral immune system, there are a variety of antibodies whose activity corresponds to environment of the local sites in which they are predominantly expressed. Immunoglobulin A (IgA) is an antibody predominantly expressed in mucosa, and acts primarily by blocking pathogen entry into epithelium. Individuals with IgA deficiencies are at dramatically increased risk of infection, reflecting IgA's role as the "first line defense" [11]. There is increased expression of IgA during the follicular phase relative to the luteal phase [3]; this pattern ultimately promotes fertility as infections early in the menstrual cycle can prevent ovulation [12]. However, at ovulation, high IgA appears to disrupt conception [13,14] by altering mucosal composition in ways that impair sperm motility [15] or, in rare cases, directly attacking sperm [16]. Accordingly, in healthy women there is a midcycle decline in IgA, corresponding to ovulation [2].

In contrast to IgA, Immunoglobulin G (IgG), the most common antibody expressed in blood, acts directly on pathogens by either lysing target cells or immobilizing and marking them for disposal [17]. Low IgG at ovulation is not associated with better reproductive outcomes [18,19], and in fact IgG may support conception by regulating systemic inflammation that is potentially damaging to a pre-placental embryo [20]. Accordingly, in healthy females, there are increases in IgG in the day prior to ovulation [2], lasting through the luteal phase [21]. Notably, although cycle variations in IgA and IgG have been primarily studied in the female reproductive tract, these effects translate into non-reproductive tract sites such as lymph nodes [22] and salivary mucosa [3].

Examining changes in IgA and IgG can reflect the relative balance of immune priorities: mucosal or/and systemic defense. Moreover, given the unique role each plays in reproduction, tracking cycle-related changes in IgA and IgG may reflect ongoing redistribution within the immune system to balance the conflicts between reproduction and immune defense [23–26]. Immunoredistribution – that is, temporary shifts that move immune cells to sites where they are most useful – can be triggered by reproductive behavior [23] such as courtship behaviors or mate competition. [27,28]. Shifting immune resources from high IgA production during the follicular phase to high IgG production at mid-to-late cycle may reflect the need to avoid disrupting conception (i.e., lowering IgA) while maintaining systemic immunity (i.e., increasing IgG). In the present study, we predicted that a decline in IgA at ovulation would correspond to an increase in IgG.

If balancing reproductive priorities is the driving force for shifts in humoral immune factors across the menstrual cycle, we would expect such shifts to be especially critical, and potentially exaggerated, in women who are sexually active relative to those who are abstinent. To date, only a few studies have examined the association between sexual activity and humoral immunity in healthy women. In one study using a sample of commercial sex workers, there was no association between frequency of sexual activity (1–3 partners daily vs. 4+ partners daily) and total IgA or IgG among HIV-negative women. However, given the very high rates of sexual activity in this sample (up to 14×/daily), there could have been a ceiling effect on degree of variation observable in humoral immune factors [29]. Another study found lower IgA levels associated with increasing frequency of sexual activity in healthy women; however, these analyses did not account for cycle phase [30]. Similarly, one study showed significantly higher IgA levels in women who were sexually abstinent as compared to women who were sexually active with a male or female partner [31]. While this study found no association between sexual activity status and cycle phase on IgA levels, *frequency* of sexual activity within sexually active participants was not considered. Finally, in a sample of male and female college students, there was a curvilinear pattern between IgA and sexual frequency, with individuals reporting sexual activity 1-2×/week showing significantly greater IgA than any other group (abstinent, <1×/week, >2×/week) [32]. However, these analyses treated both men and women in the same group, despite evidence of sex/gender differences in humoral immunity [33] and self-reported sexual frequency [34]. Collectively, these studies point to a potential effect of sexual activity on humoral immunity, but the patterns are far from clear.

The association of sexual activity and humoral immunity appears to hold regardless of the sex/gender of the sexual partner [31], and does not appear to differ between women reporting consistent vs. inconsistent condom use [29], suggesting exposure to ejaculate is not a necessary factor. Nevertheless, exposure to an intimate partner's microbiome may broadly alter immune response [35]. Thus, as an exploratory sub-analysis, we examined the potential role of barrier use in humoral immune parameters across the menstrual cycle in sexually active women. Given the presumably local effects of ejaculate on immune response, we predicted greater impact of barrier use in mucosal immunity (i.e., IgA) than systemic immunity (i.e., IgG).

In sum, we predicted that IgA would decrease at ovulation, particularly for sexually active women. Correspondingly we predicted that IgG would increase at ovulation, again, particularly for sexually active women. Finally, we predicted that, for sexually active women, exposure to ejaculate (that is, infrequent condom use) would moderate cycle-related changes in IgA, but not IgG.

2. Methods

2.1. Participants

Healthy, premenopausal women were recruited from the local community. Interested participants were screened via telephone, and again at the first lab session, to ensure they met study criteria. Exclusion criteria included: current illness or history of medical conditions known to impact immune function (e.g., cancer), use of psychoactive or immunoactive medications, use of hormonal medications (including oral contraceptives), pregnancy/lactation within the past year, and history of sexual assault (which may influence neuroendocrine response to adult sexual activity) [36]. Inclusion criteria across groups included: self-reported good health, with regular menstrual cycles (26–34 day cycles with no more than 1 missed period in the last 6 months). Sexually abstinent participants were required to report no partnered genital sexual activity in the past four months; however, participants reporting masturbation and/or lifetime history of partnered sexual activity could be included. Sexually active participants were required to report vaginal intercourse at least once per week with a single partner. As women taking hormonal contraceptives were not enrolled, sexually active participants reported using either condoms or a non-hormonal intra-uterine device as contraception.

Three participants dropped out after the first lab session, leaving 32 participants (17 sexually abstinent, 15 sexually active) in the present sample (see Table 1 for demographics). Participants were on average

Table 1
Demographics.

	Sexually active (N = 15)		Sexually abstinent (N = 17)		Total (N = 32)	
	Mean	SD	Mean	SD	Mean	SD
Age	24.96	7.05	22.16	2.85	23.56	5.54
Years of education	15.96	4.12	15.53	2.42	15.73	3.24
Body fat percentage	27.69	5.65	26.02	8.67	26.88	7.21
	N	%	N	%	N	%
Race						
White	12	80%	9	53%	21	66%
Asian	0	0%	5	29%	5	16%
Mixed race/other	3	20%	3	18%	6	18%
Ethnicity						
Hispanic/Latina	1	7%	0	0%	1	3%
Not Hispanic/Latina	14	93%	17	100%	31	97%