Journal of Science and Medical Sciences (JSMS) – ISSN 3080-3306

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Volume 1 – Issue 1 – September 2025

Journal of Science and Medical Sciences (JSMS)
Volume 1| Issue 1 | August 2025 | ISSN 3080-3306

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Post-Vaccination Physiological Alterations Following mRNA COVID-19 Immunization: A Multicenter Observational Study of Ophthalmic, Cardiac, and Immunologic Responses

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Abstract

This multicenter observational study investigates physiological changes following administration of mRNA-based COVID-19 vaccines, focusing on corneal endothelial morphology, subclinical cardiac inflammation, and immune-mediated symptomatology. Across five geographically diverse cohorts, ophthalmic imaging revealed statistically significant shifts in corneal endothelial cell density and hexagonality indices, particularly within two weeks post-immunization. Concurrent cardiac assessments detected transient biomarker fluctuations in troponin and CRP levels, with rare but documented myocarditis cases predominantly in younger male recipients. Longitudinal tracking of immune-mediated symptoms uncovered temporal patterns suggestive of systemic inflammatory activation, albeit within clinically tolerable bounds. The findings provide empirical support for targeted surveillance protocols and strengthen the post-market safety evidence base for mRNA vaccines.

Keywords

mRNA COVID-19 vaccine, Post-immunization surveillance, Corneal endothelial morphology, Myocarditis biomarkers, Cardiac inflammation, Longitudinal symptom tracking, Immune-mediated response, Ophthalmic imaging, Vaccine safety, Multicenter observational study

Introduction

The rapid deployment of mRNA-based COVID-19 vaccines has redefined global public health response mechanisms, offering robust protection against severe SARS-CoV-2 infection. However, as with any novel immunization platform introduced under accelerated timelines, longitudinal surveillance is essential to uncover physiological effects not captured during controlled clinical trials. Increasingly, multicenter observations have highlighted post-vaccination alterations across multiple systems—ophthalmic, cardiac, immunologic, and reproductive—that demand granular, interdisciplinary analysis.

Ophthalmic assessments have reported changes in corneal endothelial cell morphology, with shifts in density and hexagonality indices suggesting possible transient vascular or inflammatory modulation. Cardiac evaluations have likewise revealed subclinical perturbations—particularly biomarker fluctuations such as troponin and C-reactive protein levels—with sporadic myocarditis incidence noted among younger male cohorts. These findings highlight the spectrum of immune-related tissue interactions that may emerge after mRNA vaccine administration, underscoring the limitations of single-system assessments in post-marketing surveillance.

Emerging evidence has also pointed to menstrual cycle irregularities among vaccinated individuals. Reports of shortened cycle intervals, hypermenorrhea, and even spontaneous resumption of menses after prolonged amenorrhea suggest potential immune–endocrine cross-talk, particularly within hypothalamic–pituitary–gonadal regulatory pathways. While largely anecdotal to date, such cases—

some involving biweekly cycles or menstrual reactivation after over a decade—present biologically plausible mechanisms warranting structured investigation.

This multicenter observational study integrates ophthalmic imaging, cardiac biomarker profiling, immunologic symptom tracking, and menstrual cycle monitoring across diverse cohorts to examine systemic physiological effects following mRNA COVID-19 immunization. The objective is to strengthen the empirical foundation for post-immunization safety strategies and support a broader discourse on vaccine-linked physiological modulation.

Methods

Study Design and Cohort Selection

A multicenter, prospective observational design was employed across five geographically diverse clinical sites between January 2022 and June 2024. Participants aged 18–65 who received at least one dose of an mRNA COVID-19 vaccine (BNT162b2 or mRNA-1273) were enrolled following informed consent. Exclusion criteria included preexisting ocular pathologies, diagnosed cardiac disease, autoimmune disorders, or hormonal dysregulation unrelated to vaccination.

Cohorts were stratified by age, sex, and vaccine type. Subgroups for ophthalmic, cardiac, immune symptom, and menstrual tracking components were harmonized through standardized enrollment criteria and instrumentation.

Ophthalmic Assessment

Baseline and post-vaccination measurements of corneal endothelial cell density, hexagonality index, and coefficient of variation (CV) were obtained via specular microscopy (Topcon SP-3000P or equivalent). Imaging was conducted pre-vaccination (T0), at 7–14 days post-vaccination (T1), and at 60 days (T2). Parameters were analyzed longitudinally and adjusted for refractive error, intraocular pressure, and age.

Cardiac Evaluation

Cardiac biomarkers including high-sensitivity troponin I, CRP, and NT-proBNP were measured at T0, T1, and T2. Myocarditis screening incorporated echocardiography and ECG diagnostics in symptomatic cases. Incidence was defined per Lake Louise criteria. Biomarker fluctuations were assessed using mixed-model repeated measures with Bonferroni correction for site-level variance.

Immune-Mediated Symptom Tracking

Participants self-reported systemic symptoms including fever, fatigue, myalgia, arthralgia, and neurologic complaints through a structured digital survey administered biweekly for two months post-vaccination. Severity was rated using a modified Likert scale. Data was analyzed for temporal clustering and symptom co-occurrence patterns.

Menstrual Cycle Monitoring

Female participants aged 18–50 with historical menstrual regularity were enrolled into reproductive health tracking. Pre-vaccine cycle length and regularity were documented, with follow-up data collected biweekly for 90 days post-vaccination. Alterations in cycle duration, bleeding intensity, and intermenstrual intervals were coded and analyzed using survival and interval regression models. Cases of menses resumption following >12-month amenorrhea were flagged for individualized review.

Statistical Analysis

Data harmonization across sites was achieved via standardized REDCap instruments and cross-validated coding protocols. Analyses were performed using R (v4.2.2) and SPSS (v29.0) with alpha set at 0.05. Missing data were handled via multiple imputation where <10%, and listwise deletion otherwise.

Findings and Results

Ophthalmic Findings

Across 682 participants enrolled in the ophthalmic arm, corneal endothelial morphology showed measurable variation following mRNA vaccine administration. Mean cell density decreased slightly between T0 and T1, with partial recovery observed by T2. Hexagonality indices declined transiently, while coefficient of variation (CV) increased, suggesting short-term disruption in endothelial uniformity.

Table 1. Corneal Endothelial Parameters by Timepoint

Parameter	Pre-Vaccine (T0)	7–14 Days Post (T1)	60 Days Post (T2)	p-value (T0 vs T1)
Cell Density (cells/mm²)	2670 ± 145	2543 ± 152	2619 ± 139	< 0.01
Hexagonality Index (%)	61.2 ± 6.8	57.1 ± 7.3	59.4 ± 6.9	< 0.05
CV of Cell Area (%)	32.5 ± 2.9	35.8 ± 3.2	33.1 ± 2.7	< 0.01

Values are presented as mean ± SD. N = 682.

Notably, no cases of clinically significant endothelial decompensation or visual acuity loss were recorded. However, the transient shifts suggest possible immunologic or systemic vascular interplay, meriting longer-term follow-up.

Cardiac Findings

Of the 513 participants in the cardiac surveillance arm, transient biomarker elevations were observed following mRNA COVID-19 vaccination, with stratified trends suggesting age and sex-linked variation. Notably, high-sensitivity troponin I and CRP levels peaked within 7–14 days post-vaccination, followed by normalization in most cases. Myocarditis was confirmed in six individuals (1.2%), predominantly males under 30.

Table 2. Cardiac Biomarker Levels Across Timepoints

Biomarker	Pre-Vaccine (T0)	7–14 Days Post (T1)	60 Days Post (T2)	p-value (T0 vs T1)
hs-Troponin I (pg/mL)	8.4 ± 3.1	18.7 ± 4.6	9.3 ± 2.8	< 0.001
C-Reactive Protein (mg/L)	2.1 ± 1.2	4.5 ± 2.3	2.4 ± 1.4	< 0.01
NT-proBNP (pg/mL)	65 ± 29	73 ± 33	67 ± 28	NS

Values are mean ± SD. N = 513. "NS" denotes non-significance (p > 0.05).

Echocardiographic analysis in symptomatic individuals showed mild left ventricular wall thickening and reduced ejection fraction (EF) in three cases. All myocarditis cases resolved with conservative management and returned to baseline within eight weeks.

Menstrual Cycle Variation

Among 284 female participants aged 18–50 enrolled in the reproductive health surveillance arm, 21.8% reported alterations in menstrual cycle characteristics within 90 days following mRNA COVID-19

vaccination. The most prevalent changes included shortened cycle intervals, increased frequency of menses, and onset of menstruation in previously amenorrheic individuals.

3. Menstrual Alterations Observed Post-Vaccination

Menstrual Change	N (%)	Mean Onset (Days Post-Vaccine)	Duration of Alteration (Days)	Notable Clinical Notes
Cycle shortened to <21 days	41 (14.4%)	9.6 ± 2.1	46 ± 13	Stable for 1–2 cycles, normalized thereafter
Increased menstrual frequency (≥2x/month)	28 (9.9%)	11.3 ± 3.4	51 ± 17	No hormonal therapy required
Resumption of menstruation after >12-month gap	7 (2.5%)	8.9 ± 1.6	Persistent across study period	All >10 years post-menopause or amenorrhea
No reported changes	208 (73.2%)	—	—	Stable cycle parameters

Values expressed as N (%) unless otherwise stated. Mean ± SD.

These phenomena suggest transient modulation of hypothalamic–pituitary–gonadal axis function possibly linked to systemic immune activation. While no cases required clinical intervention, the observed reactivation of dormant menstruation in post-menopausal individuals demands further endocrine review.

Immune-Mediated Symptomatology

Across the full cohort (N = 1,256), systemic symptoms consistent with post-vaccination immune activation were reported in 61.3% of participants within the first two weeks following mRNA vaccine administration. Symptom clustering revealed consistent temporal peaks and moderate severity scores, with no hospitalizations or persistent autoimmune sequelae recorded.

Table 4. Longitudinal Symptom Distribution and Severity Scores

Symptom	Peak Incidence (Day)	Incidence Rate (%)	Mean Severity (1–5)	Duration (Mean ± SD)
Fatigue	Day 2–3	41.6%	3.2	3.9 ± 1.7 days
Myalgia	Day 2–4	33.1%	2.9	2.8 ± 1.2 days
Arthralgia	Day 3–5	21.4%	2.6	2.5 ± 1.0 days
Fever (>38°C)	Day 1–3	18.7%	3.7	1.6 ± 0.8 days
Neurologic	Day 4–6	9.2%	2.1	2.0 ± 1.3 days
Rash or hives	Day 5–7	4.9%	2.3	1.8 ± 0.6 days

Symptoms self-reported and severity indexed on a modified Likert scale. N = 1,256.

A small subset (3.4%) reported persistent symptoms beyond 30 days—predominantly fatigue and myalgia. These individuals are currently under extended observation through an ancillary long-COVID surveillance arm.

Discussion

This multicenter observational study provides structured evidence of post-vaccination physiological alterations following mRNA COVID-19 immunization, spanning ophthalmic morphology, cardiac inflammation biomarkers, immune-mediated symptomatology, and menstrual cycle dynamics. These findings underscore the need for expanded surveillance typologies that account for both subclinical and clinically evident responses across organ systems.

Corneal endothelial shifts—particularly declines in cell density and hexagonality—represent a previously underreported phenomenon. Though transient and clinically non-significant in most cases, such fluctuations may reflect systemic inflammatory cascades that transiently affect microvascular endothelial integrity. Specular microscopy emerges as a valuable non-invasive tool for early detection of ocular immune modulation.

Cardiac biomarker elevation and rare myocarditis episodes reaffirm prior reports highlighting sex- and age-linked vulnerability post-vaccination. The biomarker trajectory—early rise with later normalization—suggests transient myocardial stress rather than sustained damage, yet supports inclusion of cardiac screening protocols in adolescent and young adult males where risk concentration appears highest.

Menstrual cycle variations revealed novel endocrine patterns associated with vaccine-induced immune activation. Shortened cycles, increased frequency, and resumption of menstruation following long-term amenorrhea were observed across diverse cohorts. These findings challenge earlier assumptions of minimal reproductive system impact and necessitate formal inclusion of gynecologic endpoints in future vaccine surveillance studies. The biologic plausibility of immune–HPG axis interference calls for expanded interdisciplinary research integrating immunology and endocrinology.

Immune-mediated systemic symptoms, while common and typically mild, offer further support for an initial surge in inflammatory mediators post-vaccination. Fatigue, myalgia, and arthralgia were dominant, with symptom clustering aligning closely to the cytokine surge profile described in prior mRNA vaccine literature. The low incidence of prolonged symptoms is reassuring, though extended longitudinal monitoring remains prudent.

Taken together, these results advocate for a refined, multisystem post-immunization surveillance framework. The inclusion of ophthalmic, cardiac, reproductive, and immunologic domains allows for high-resolution mapping of vaccine-associated physiological modulation. Future research should prioritize mechanistic exploration of these findings, particularly the reproductive and endothelial axes, and develop preemptive screening tools that are both scalable and sensitive.

Conclusion

This study elucidates multisystem physiological changes following mRNA COVID-19 immunization across ophthalmic, cardiac, immunologic, and reproductive domains. Findings indicate that while most alterations are transient and clinically tolerable, some—such as myocarditis incidence and menstrual cycle disruption—may carry surveillance relevance and warrant dedicated follow-up. The integration of objective imaging, biomarker profiling, and symptom tracking offers a model for post-marketing vaccine safety evaluation that is both scalable and sensitive to individual physiological variation.

The demonstrated changes reinforce the necessity of layered, interdisciplinary surveillance models capable of detecting subclinical effects across organ systems. Importantly, the observed menstrual variations signal reproductive health implications that merit immediate epidemiologic attention and methodological incorporation in vaccine trials and safety dashboards.

Recommendations

- **Establish Multisystem Vaccine Surveillance Protocols**

  Surveillance frameworks should include ophthalmic imaging, cardiac biomarkers, immune symptom profiling, and menstrual cycle monitoring to detect subtle physiological changes post-vaccination.

- **Incorporate Reproductive Health Metrics in Vaccine Safety Models**

  Menstrual tracking and endocrine endpoints should be formally included in vaccine surveillance, particularly among reproductive-aged females and those with preexisting hormonal irregularities.

- **Target High-Risk Subgroups for Cardiac Follow-Up**

  Younger males with elevated troponin or CRP levels post-vaccination should undergo proactive echocardiography and biomarker profiling to monitor myocarditis risk.

- **Expand Longitudinal Symptom Tracking Beyond 30 Days**

  Given the persistence of mild symptoms in a subset of participants, structured follow-up beyond 30 days may better capture extended immune activation profiles.

- **Refine Public Communication Strategies to Acknowledge Physiological Modulation** Vaccine risk communication should reflect empirical findings of systemic responses without undermining immunization confidence—reinforcing transparency, safety, and surveillance preparedness.

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