

**THE AUTHORS REPLY:** In response to Stanford et al.: after the exclusion of patients receiving insulin, the median gestational weight gain among the women in our study was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2],  $P<0.001$ ). In an evaluation of changes in postpartum weight from the initial antenatal visit, the median gestational weight loss was higher in the metformin group than in the placebo group (1.9 kg [interquartile range, -5.1 to 0.2] vs. 0 kg [interquartile range, -3.9 to 1.5],  $P=0.02$ ). We agree that metformin might reduce the risk of long-term obesity in these women.

In response to Sahin and Corapcioglu: the American Diabetes Association classifies metformin as a category B drug (i.e., no evidence of risk in humans) during pregnancy. In the United Kingdom, metformin is recommended by the National Institute for Health and Care Excellence.<sup>1</sup> There is no evidence of an increase in congenital malformations (including testicular abnormalities or defects in growth or motor development) in babies born to mothers treated with metformin.<sup>2,3</sup> Blood-pressure results in a large cohort of 2-year-old children showed no differences between those whose mothers had received insulin and those whose mothers had

received metformin.<sup>4</sup> Active B<sub>12</sub> (holotranscobalamin) and methylmalonic acid are better measures of vitamin B<sub>12</sub> status than are serum levels and do not appear to be pathologically altered in patients with type 2 diabetes after metformin treatment.<sup>5</sup>

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Since publication of their article, the authors report no further potential conflict of interest.

1. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. August 2015 (<https://www.nice.org.uk/guidance/ng3>).

2. Bolton S, Cleary B, Walsh J, Dempsey E, Turner MJ. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. *Eur J Pediatr* 2009;168:203-6.

3. Cassina M, Donà M, Di Gianantonio E, Litta P, Clementi M. First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20:656-69.

4. Battin MR, Obolonkin V, Rush E, Hague W, Coat S, Rowan J. Blood pressure measurement at two years in offspring of women randomized to a trial of metformin for GDM: follow up data from the MiG trial. *BMC Pediatr* 2015;15:54.

5. Obeid R, Jung J, Falk J, et al. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. *Biochimie* 2013;95:1056-61.

DOI: 10.1056/NEJMc1603067

## Transient Smartphone “Blindness”

**TO THE EDITOR:** Transient monocular vision loss is a common clinical presentation, and the cause is not always thromboembolic.<sup>1</sup> We present two cases in which careful history taking established a benign cause (for the case histories, see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

A 22-year-old woman presented with a several months' history of recurrent impaired vision in the right eye that occurred at night. The results of ophthalmic and cardiovascular examinations were normal. Vitamin A levels and the results of magnetic resonance angiography, echocardiography, and a thrombophilia screening were also normal.

The second case involved a 40-year-old woman

who presented with a 6-month history of recurrent monocular visual impairment on waking, lasting up to 15 minutes. The results of investigations for a vascular cause were again normal. Aspirin therapy had been commenced.

When the patients were seen in our neuro-ophthalmic clinic, detailed history taking revealed that symptoms occurred only after several minutes of viewing a smartphone screen, in the dark, while lying in bed (before going to sleep in the first case and after waking in the second). Both patients were asked to experiment and record their symptoms. They reported that the symptoms were always in the eye contralateral to the side on which the patient was lying.

We hypothesized that the symptoms were due

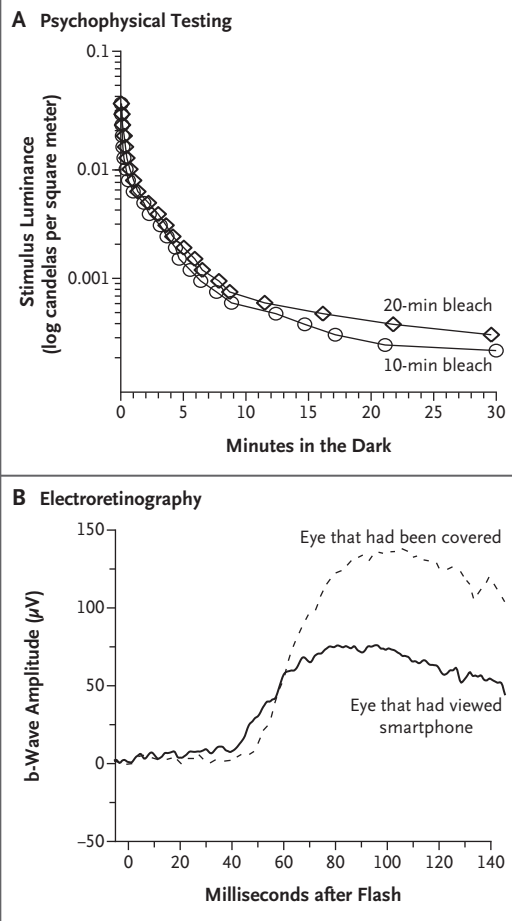
**Figure 1. Diminished Retinal Sensitivity after Smartphone Viewing.**

In Panel A, the points plot visual threshold as a function of time after 10 or 20 minutes of smartphone viewing. The y axis plots the minimum intensity of light that the participant was able to see in the dark. Initially, the participant required a higher-intensity stimulus, indicating low sensitivity; after approximately 20 minutes, the participant was able to see stimuli 100 times dimmer. In Panel B, the two traces show averaged electroretinographic responses to a dim flash of light that was delivered within a few minutes after 20 minutes of monocular smartphone viewing. The response amplitudes are very different, indicating that the eye that had viewed the smartphone had much lower retinal sensitivity than the eye that had been covered (this interocular difference is what the patients perceived as transient monocular blindness). After approximately 20 minutes, responses from both eyes were very similar (see the Supplementary Appendix).

to differential bleaching of photopigment, with the viewing eye becoming light-adapted while the eye blocked by the pillow was becoming dark-adapted. Subsequently, with both eyes uncovered in the dark, the light-adapted eye was perceived to be “blind.” The discrepancy lasted several minutes, reflecting the time course of scotopic recovery after a bleach.<sup>2-4</sup>

In a study approved by a research ethics committee, two of the authors monocularly viewed a smartphone screen at arm's length and quantified the time course of recovery of sensitivity in the dark both psychophysically and electrophysiologically (Fig. 1). Visual sensitivity was appreciably reduced after smartphone viewing, taking several minutes to recover, and this reduction in sensitivity was measurable at the level of the retina (Fig. 1B).

Although most people view screens binocularly, people frequently use smartphones while lying down, when one eye can be inadvertently covered. Smartphones are now used nearly around the clock, and manufacturers are producing screens with increased brightness to offset background ambient luminance and thereby allow easy reading. Hence, presentations such as we describe are likely to become more frequent. Our cases show that detailed history taking and an understanding of retinal physiology can reassure both patient and doctor and can avoid unnecessary anxiety and costly investigations.



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Supported by a Fight for Sight (United Kingdom) grant (to Dr. Mahroo).

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Petzold A, Islam N, Hu HH, Plant GT. Embolic and non-embolic transient monocular visual field loss: a clinicopathologic review. *Surv Ophthalmol* 2013;58:42-62.
2. Hecht S, Haig C, Chase AM. The influence of light adaptation on subsequent dark adaptation of the eye. *J Gen Physiol* 1937; 20:831-50.
3. Lamb TD, Pugh EN Jr. Dark adaptation and the retinoid cycle of vision. *Prog Retin Eye Res* 2004;23:307-80.
4. Cameron AM, Mahroo OA, Lamb TD. Dark adaptation of human rod bipolar cells measured from the b-wave of the scotopic electroretinogram. *J Physiol* 2006;575:507-26. DOI: 10.1056/NEJMc1514294

## Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

**TO THE EDITOR:** Resistance to all antimicrobial agents has developed in some *Neisseria gonorrhoeae* strains. Dual antimicrobial therapy (ceftriaxone plus azithromycin) is a recommended first-line empirical treatment in many countries.<sup>1-3</sup> We describe treatment failure with dual therapy in a patient with gonorrhea.

In December 2014, a heterosexual man presented to a sexual health clinic in the United Kingdom with a 2-week history of urogenital symptoms (Table 1). Ten days previously, he had returned from Japan, where his Japanese female partner had been treated for gonorrhea. He reported having no other recent sexual partners.

*N. gonorrhoeae* was detected in a urine specimen and pharyngeal swab on nucleic acid amplification testing (Abbott RealTime CT/NG assay) and in a culture of a urethral specimen. All *N. gonorrhoeae*-positive specimens on nucleic acid amplification testing were also confirmed as positive with the use of a duplex polymerase-chain-reaction (PCR) assay targeting the *porA* pseudogene and *opa* genes. According to the local laboratory, testing with the disk-diffusion method showed that the *N. gonorrhoeae* strain was resistant to cefuroxime, ciprofloxacin, and tetracycline. The patient declined to undergo testing for syphilis and human immunodeficiency virus infection.

The patient received one dose of ceftriaxone intramuscularly at a dose of 500 mg plus 1 g of azithromycin orally.<sup>3</sup> At the test of cure on day 15, a urine specimen was negative, but a pharyngeal swab remained positive for *N. gonorrhoeae* on the identical nucleic acid amplification test. The patient reported that he did not have sexual contact after treatment, and he did not return until day 79, when a pharyngeal swab was positive for *N. gonorrhoeae* on the nucleic acid amplification test.

On day 98, *N. gonorrhoeae* was detected in a pharyngeal sample on the nucleic acid amplification test and culture. The patient received one dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g orally.<sup>3</sup> At the test of cure on day 112, the pharyngeal specimen was negative (according to the nucleic acid amplification test). Initial pre-treatment specimens were unavailable for further analysis.

The *N. gonorrhoeae* species was verified with the use of the Phadebact Monoclonal GC Test and matrix-assisted laser desorption/ionization-time of flight mass spectrometry. Antimicrobial susceptibility testing with the use of Etest showed that the strain was resistant to ceftriaxone, azithromycin, cefixime, cefotaxime, penicillin, tetracycline, and ciprofloxacin, but it was susceptible to spectinomycin. Whole-genome sequencing of one isolate with the use of Illumina MiSeq (BioProject accession number PRJNA305360) and conventional sequencing identified *N. gonorrhoeae* multilocus sequence type ST1901 and a new *N. gonorrhoeae* multiantigen sequence type ST12133 in all specimens (the isolate and PCR specimens). Resistance determinants,<sup>1</sup> mosaic penicillin-binding protein 2 X (which decreases ceftriaxone target affinity), deletion of one adenine in the *mtrR* promoter (which increases MtrCDE efflux of ceftriaxone and azithromycin), and *penB* (which decreases PorB influx of ceftriaxone and azithromycin) were detected in all specimens.

The patient was considered to have treatment failure because the post-treatment isolate was resistant to ceftriaxone and azithromycin, all specimens contained resistance determinants and identical sequence types, and reinfection was deemed to be unlikely. The *N. gonorrhoeae* strain that caused the failure belonged to the identical *N. gonorrhoeae* multiantigen sequence