

Farewell to indigo carmine

➔ With a nationwide shortage of this marker dye, what are the options, and cautions, for obstetricians and gynecologists?



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Suddenly, indigo carmine is in short supply throughout the United States. One manufacturer has stopped production because of a raw materials shortage; another is experiencing manufacturing delays. Neither company can estimate a resupply or product return date.¹

Indigo carmine is approved by the US Food and Drug Administration (FDA) to localize ureteral orifices during cystoscopy and is commonly used in obstetrics and gynecology as a marker dye in the following additional situations:

- administered in a dilute solution via a catheter to back fill the

bladder and test for bladder injury

- administered via a cannula in the uterine cavity to test the patency of the fallopian tubes
- injected into the amniotic fluid compartment to test for premature rupture of the membranes (PROM)
- injected into the amniotic fluid of a twin gestation to mark the amniotic fluid of one twin.

With this agent in short supply, we need to identify alternative marker dyes to use in our clinical practice. In this editorial, I provide a list of possible options to replace indigo carmine. Evidence supporting the use and safety of marker dyes in obstetrics and gynecology is based on small cohorts or case reports. The available evidence is of modest to low quality, and it is especially challenging to identify uncommon adverse effects. Consequently, expert opinion guides most practice recommendations.

Options to test the function of the ureters at cystoscopy

Given the lack of availability of indigo carmine, I recommend one of the following three options to test the function of the ureters at cystoscopy.

Partially fill the bladder with a solution of either sterile water or a 10% dextrose solution. (Experienced surgeons may prefer to use saline.) The turbulence of the

interaction between the ureteral urine jet and instilled fluid in the bladder may permit visualization of the urine stream exiting the ureteral orifices as it swirls through the sterile water or dextrose solution. Both sterile water and a 10% dextrose solution offer a contrast in viscosity between the urine and the cystoscopy fluid, which may enhance the ability to detect the urine jet leaving the ureter.²

Administer IV methylene blue. Methylene blue is FDA approved for methemoglobinemia treatment. For this indication, it is administered intravenously at a dose of 1 to 2 mg/kg over 5 to 10 minutes. Paradoxically, when administered at a dose of >7 mg/kg, methylene blue can cause methemoglobinemia.³

Methylene blue often is provided as a 1% solution of 10 mg/mL in 10-mL vials. To use intravenous (IV) methylene blue to test ureteral function at cystoscopy, administer IV methylene blue 50 mg over 5 minutes. Use the cystoscope to view the colored urine exiting the ureteral orifices.^{4,5} Administering a small dose of IV furosemide may accelerate the appearance of methylene blue in the urine.

When to use caution. Methylene blue blocks serotonin metabolism by inhibiting monoamine oxidase and may precipitate a **serotonin**

Instant Poll



Is your institution experiencing a shortage of indigo carmine? What is your advice to readers about alternatives to its use?

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syndrome in patients taking selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or monoamine oxidase inhibitors (MAOIs).

Common findings in the serotonin syndrome include: temperature above 38° C (100.4° F), anxiety, agitation, delirium, clonus, tremor, and hypertonia.⁶ I recommend that you **DO NOT** use IV methylene blue in patients taking these medications.^{7,8}

Great caution should be used before administering IV methylene blue in the presence of the following clinical situations:

- renal impairment
- G6PD deficiency
- pediatric patients.

Methylene blue **never** should be given by a subcutaneous or intrathecal route. In pregnant women it should **never** be injected into the amniotic fluid compartment.

Use preoperative oral phenazopyridine. If the preoperative plan includes a cystoscopy procedure to test ureteral function, administering oral phenazopyridine in the preoperative holding area will result in colorization of the urine within 30 minutes, and it will persist for approximately 4 to 5 hours. To use this approach, administer one dose of phenazopyridine (Pyridium, Azogestic), 100 mg or 200 mg orally, 30 minutes to 1 hour before the planned surgical start time, in the preoperative holding area.⁹ During cystoscopy, the urine from the ureteral jet will be colored orange.

When to use caution. Phenazopyridine should not be administered to patients with G6PD deficiency.

Option to test for bladder injury

Methylene blue. If methylene blue is used to test the integrity of

the bladder, I recommend diluting 10 mg methylene blue in 1 L normal saline and then instilling the dilute solution through a catheter into the bladder.¹⁰

It is unlikely that this technique will be associated with sufficient methylene blue absorption to cause a serotonin syndrome. Therefore, this technique can be used in patients taking SSRIs, SNRIs, and MAOIs.

Option to test patency of the fallopian tubes (chromopertubation)

Methylene blue. If methylene blue is used via a cannula in the uterine cavity to test the patency of the fallopian tubes, I recommend diluting 10 mg methylene blue in 150 mL normal saline and using the dilute solution to test tubal patency.

It is unlikely that this process will lead to sufficient methylene blue absorption to cause a serotonin syndrome. Therefore, this technique can be used in patients taking SSRIs, SNRIs and MAOIs. However, if intrauterine injection of the dilute dye solution results in extravasation of the dye into the pelvic veins, a significant amount of dye can enter the circulation.¹¹ There are case reports of anaphylaxis following intrauterine injection of methylene blue to test tubal patency.^{12,13}

Options to diagnose PROM and to use for twin amniocentesis

None. Most experts recommend against the intra-amniotic injection of methylene blue to diagnose PROM or in twin amniocentesis procedures. Methylene blue injected into the intra-amniotic fluid during amniocentesis in multiple gestations has been reported to cause fetal bowel obstruction or atresia.^{14,15}

Fetal death also has been reported.¹⁶ Decades ago, indocyanine green, which is FDA approved to determine cardiac output, liver blood flow, and hepatic function, was reported to be useful to mark one sac of a twin gestation during amniocentesis.¹⁷ With modern ultrasonography technology, the need to rely on a dye to mark a sac of a twin has decreased significantly.

Our only option is to cope—effectively as possible

Over decades, the medical community develops patterns of patient care that are critically dependent on the availability of key pharmaceuticals and devices. When a pharmaceutical or device suddenly becomes unavailable, it can disrupt important patterns of patient care. Imagine the impact on obstetrics practice if oxytocin became unavailable due to manufacturing shortages. Likely, both market forces and government regulation are the root cause of the shortfalls. Preventing the adverse consequences of the sudden loss of key pharmaceuticals and devices is an important priority to ensure optimal care of our patients. 📌



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Dr. Barbieri reports no financial relationships relevant to this article.



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Editorial

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