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Medical Devices Safety Update

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In this issue

Be aware of cross-reactivity with home-use self-test ovulation kits

Cross-reactivity of human chorionic gonadotropin with self-test ovulation kits may result in false positive results and care is needed when using them in conjunction with some procedures and ovulation inducing agents.

The TGA's laboratories recently tested one ovulation self-test device which passed regarding its sensitivity to luteinising hormone (LH) at 50 mIU/mL, but failed specificity testing at 200 mIU/mL, as it produced a positive result in the presence of human chorionic growth hormone (hCG). The sponsor subsequently cancelled the Australian Register of Therapeutic Goods entry as a result of the test results.

Medical Devices Safety Update discussed issues around sensitivity and specificity in March 2014.

Hormone surge

Self-test ovulation kits monitor changes in LH, with a surge in the hormone indicating the upcoming occurrence of ovulation. This LH surge occurs about 36 hours before ovulation. The LH surge appears in urine about 12 hours after appearing in serum, noting that the surge appears in pulses, rather than as a steady release.

During pregnancy LH is suppressed by oestrogen and progesterone, both of which are increased by human chorionic gonadotropin (hCG; a hormone secreted into maternal circulation after implantation, which occurs 6-12 days after ovulation).

Pregnancy increases the level of hCG which can cross-react with LH self-tests to falsely appear as a surge in LH. Some studies have shown cross reactivity between low levels of hCG and LH in home-use LH detection kits, but this does not appear to be explicitly stated in the Instructions for Use for these kits.

Self-test ovulation kits may be used to increase the chance of conception with the timing of intercourse, or intrauterine insemination (IUI) as an infertility treatment, shortly after the LH surge.

Although the use varies in each setting, if the progesterone level indicates that ovulation occurred, and the women's cycles are regular, there may be a role for the LH tests to assist in timing of intercourse, although most guidelines state that the most reliable way to time intercourse is for intercourse to occur every 2-3 days.

If a woman is engaged with a fertility clinic and undergoing work up for IUI (usually due to male factor infertility) she will either be following her natural cycle or undergoing ovulation induction. Part of a common protocol appears to be the use of daily home ovulation test kits, followed by a confirmatory blood test prior to the final steps before IUI. The confirmatory blood test is likely to be for serum LH, which if suppressed will raise suspicion of early pregnancy.

Don't rely solely on LH tests

Solely relying on home-use LH tests to determine the timing of an IUI procedure or the use of ovulation inducing agents has a potential to add

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TGA Health Safety Regulation

additional risks for women who are in early stages of pregnancy, as a test kit's cross-reactivity with hCG could falsely appear to be a surge in the pre-ovulation marker. One such situation was described by US researchers in the journal *Clinical Biochemistry* in 2013:[1]

> *A 37 year old female who was being treated for infertility underwent intrauterine insemination (IUI). Two weeks later the patient thought she began menses and began Clomid (clomiphene citrate; an ovulation inducing agent) and home testing for a luteinizing hormone (LH) surge. Fourteen days after her last menstrual period a home ovulation prediction device (LH device) was positive and she scheduled an appointment for IUI. Nine days later, the patient presented with vaginal bleeding and severe pelvic pain. A quantitative serum hCG test was positive and transvaginal ultrasound demonstrated a 6 week pregnancy with a hemorrhagic cyst. She underwent surgery to stop the bleeding, and subsequently lost the pregnancy ...*
>
> *In the early days of immunoassay, cross reactivity between LH and hCG was a problem. Today however, cross reactivity in quantitative assays is extremely low. This study demonstrates that qualitative LH devices may produce false positive results in women who are very early in pregnancy. Package inserts for some devices contain a cautionary statement which states that "results obtained during pregnancy or administration of certain drugs including hCC may produce misleading results"; however, it is clear that most physicians and laboratorians are unaware of any potential cross-reactivity. Physicians that rely on home LH devices to time IUI should instruct their patients to use devices with minimal hCC cross-reactivity.*

Pregnancy a contraindication

Several ovulation inducing agents list pregnancy as a contraindication in their Product Information and some are known to be embryotoxic, fetotoxic, and associated with birth defects and marked post-implantation loss if used during early pregnancy.

It is important to note that the only time that there is a risk of inadvertently using ovulation inducing agents or IUI during early pregnancy is the first cycle, as subsequent cycles will have a pregnancy test done to assess the success of the cycle prior. This initial cycle is often commenced in the first two days of a normal period, usually indicating that conception has not occurred in the month prior.

As LH tests are available off the shelf, consumers may use them without medical supervision to assist with the timing of intercourse. In this scenario there is no risk of taking ovulation inducing agents or undergoing IUI inadvertently during early pregnancy.

REFERENCE

1 Clin Biochem. 2013 Oct;46(15):1625. doi: 10.1016/j.clinbiochem.2013.07.017. Epub 2013 Jul 27.

TGA undertakes product safety review into intragastric balloon systems

The TGA has conducted a product safety review of two intragastric balloon systems included on the Australian Register of Therapeutic Goods.

The TGA's review follows information published by the USA Food and Drug Administration (FDA) about deaths and serious injuries to patients associated with use of intragastric balloons to treat obesity.

Intragastric balloon systems involve endoscopic insertion of a balloon into the stomach and inflation of the balloon with liquid. The space-occupying fluid-filled balloon aims to achieve temporary weight loss by delaying gastric emptying, which can create a feeling of fullness.

The TGA has received 19 adverse event reports since 2009 regarding the intragastric balloon systems that are currently being supplied in Australia. These reports include three patient deaths.

In conducting the review TGA asked the sponsors of the intragastric balloons to provide:

- post-market safety data

- the current Instructions for Use
- a clinical evaluation report
- risk assessment documentation.

The information requested has undergone review and the TGA is working with sponsors and manufacturers to ensure clinicians and patients are fully informed of the risks with this type of device.

The FDA has similarly approved new labelling which adds information to the Instructions for Use about certain adverse events and the effects of these events including death.

Advice for health professionals

If you are treating a patient who has an intragastric balloon be alert to symptoms that might indicate there is an issue associated with the device. Adverse events associated with these devices include:

- obstruction
- ulceration
- necrosis
- ischaemia (gastric or intestinal)
- spontaneous hyperinflation of the balloon
- perforation (oesophageal, gastric or intestinal)
- gastritis/gastric erosions
- acute pancreatitis.

The TGA recommends that you ensure the intragastric balloon is not inserted where contraindications exist. Refer to the Instructions For Use for the complete list of contraindications.

Where relevant, patients should be advised to take the necessary precautions to prevent pregnancy prior to placement and throughout the duration of treatment, and be instructed to inform you as soon as possible if pregnancy is confirmed during treatment, so that removal of the device can be arranged.

The TGA recommends that you monitor patients closely during the entire term of treatment with intragastric balloon systems for possible complications. In particular, please be aware that patients with an intragastric balloon who present with severe abdominal pain and have a negative endoscopy and x-ray, may still require a CT scan to definitively rule out a perforation.

What to report? Please report adverse events, as well as near misses

The TGA encourages the reporting of any suspected adverse event or potential adverse event relating to a medical device. Adverse events can involve actual harm to a patient or caregiver, or a near miss that may have resulted in harm.

Some issues relating to medical devices that may lead to adverse events and prompt you to report include:

- mechanical or material failure
- design issues
- labelling, packaging or manufacturing deficiencies
- software deficiencies
- device interactions
- user/systemic errors

Suspected adverse events or near misses can be reported directly to the TGA:

- **online** at www.tga.gov.au (click 'Report a problem')
- **by emailing** iris@tga.gov.au
- **by mail** to IRIS, TGA, PO Box 100, Woden ACT 2606
- **by fax** to 02 6203 1713

For more information about reporting, visit www.tga.gov.au or contact the TGA's Medical Devices Branch on 1800 809 361.

For the latest information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medical Devices Safety Update, contact the TGA's Medical Devices Branch at iris@tga.gov.au or 1800 809 361

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