Dr Ladouceur appeals for a return to artful care, in which evidence does not interfere with clinical judgment. I remind Dr Ladouceur that evidence-based care occurs at the intersecting triad of clinician judgment, best available evidence, and patient values and preferences, all of which underlie the shared decision-making paradigm.[22] In mourning the loss of a pointless and potentially harmful routine examination, despite clear values and preferences expressed by women and evidence that it would harm but not benefit women, Dr Ladouceur is not making the case for clinical judgment versus evidence. Rather he has made a case for his personal judgment, which does not appear to be shared by patients or by guideline panels in Canada and the United States.

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Outdated approach to a common problem

As a primary care provider with a strong women's health practice that includes obstetrics and low-intervention fertility treatment, I was happy to see a discussion of clomiphene citrate by Davidson et al in the June 2016 issue of *Canadian Family Physician*.[1] While adequately researched, the authors' paper does not fully communicate the small but important risks of clomiphene use and its side effects, nor does it accurately reflect the clinical practice of treatment for anovulatory infertility in Canada today. Further, although letrozole is mentioned, the use of letrozole for ovulation induction is not discussed, and the authors fail to mention that letrozole has a higher rate of pregnancy, lower rate of multiples, and lower risk of intrauterine growth restriction for babies conceived compared with clomiphene.

Although the authors correctly identify the small risk of ovarian hyperstimulation syndrome (OHSS) with clomiphene, they do not convey the seriousness of this complication. Although most cases of OHSS can be monitored closely and treated in an outpatient setting, more serious cases require hospital admission and monitoring.[2] Complications of OHSS can include renal failure, thromboembolism, and adult respiratory distress syndrome, all of which are life threatening.[2] The risk of OHSS is low but is increased in women who are younger (<30 years of age), have polycystic ovary syndrome, and conceive during the treatment cycle.[2] Therefore, the risk is greatest in patients who are the best candidates for clomiphene treatment and, for these patients, the risk is likely greater than the 2 in 1095 quoted by the authors from a meta-analysis of a heterogeneous population. Although most patients who develop OHSS while taking clomiphene will have a mild case, this risk should not be underappreciated or dismissed.

The authors mention a risk of multiple pregnancy from clomiphene of 6% based on a randomized controlled trial. This is lower than a more recently published risk of 11.7% for twin birth and of 1.1% for triplet or quadruplet birth.[3] The risk of higher-order multiples was not communicated by the authors and is a considerable risk for patients and their offspring. Although uncommon, a 1% risk of higher-order multiples is an important risk for anyone prescribing clomiphene to be aware of and to adequately counsel patients about selective reduction should higher-order multiples occur.

The authors also failed to mention additional risks of clomiphene citrate including thinning of the endometrial lining, a risk that increases over time owing to the antiestrogen side effects and long half-life of clomiphene.[4] Although the importance of this is controversial,[5] the fertility community believes it decreases the probability of pregnancy, it might contribute to fetal risks including intrauterine growth restriction, and identification of this side effect should prompt consideration of alternative treatment. Other side effects not mentioned include mood swings,[6] vasomotor symptoms, and visual disturbances.[7] Development of visual disturbances is considered a contraindication to use of clomiphene and it is recommended to stop use immediately if they occur.[8]

Current clinical practice for the treatment of anovulatory infertility in Canada does include the use of clomiphene citrate and the authors are accurate in stating this is recommended as first-line treatment according to a Society of Obstetricians and Gynaecologists of Canada guideline published in 2010.[9] However, the American College of Obstetricians and Gynecologists released a committee opinion in June 2016 stating that

> for women with polycystic ovary syndrome and a body mass index greater than 30, letrozole should be considered as first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate.[10]

In practice, most providers of fertility care use clomiphene citrate as well as letrozole as first-line therapy for ovulation induction depending on various factors, including patient preference.

The authors' suggestion to use clomiphene for "6 cycles before considering alternate methods of ovulation induction"[1] is based on a paper published in 1997 and is quite outdated. Although the Society of Obstetricians and Gynaecologists of Canada and American Society for Reproductive Medicine support its use for up to 6 cycles,[8,9] most clinicians in practice do not pursue more than 3 cycles of clomiphene owing to the risk of multiples, mediocre probability of conception, and availability of other, safer, and more effective options. Specifically, the probability of pregnancy per cycle of clomiphene has been reported to be as high as 19.3% versus 26.3% with letrozole.[11] The risk of twins is lower with letrozole[12] and to date there has only been 1 case of triplets.[13]

Therefore, most clinicians will try another ovulatory induction agent, usually letrozole, after 1 to 3 but rarely as many as 6 cycles of clomiphene. This is supported by a study in which most physicians surveyed reported use of letrozole for ovulation induction despite current US Food and Drug Administration warnings.[14]

The authors are correct in stating that letrozole is not approved for treatment of infertility in Canada. However,

this does not mean letrozole is not safe for this use. The safety of letrozole has been well established[15] and it is considered as safe as, if not safer than, clomiphene by Motherisk.[16] Specifically, Gill et al conclude

> compared with clomiphene citrate, letrozole appears to be a more favourable first-line treatment to induce ovulation, as it is associated with higher pregnancy rates and has fewer unfavourable side effects than clomiphene citrate, such as the potential for intrauterine growth restriction.[16]

This is believed to be owing, in part, to the shorter half-life of letrozole, which reduces the effect on endometrial thickness and reduces the amount detectable in early pregnancy compared with clomiphene. Once again, these and other authors conclude that letrozole has a greater probability of pregnancy per cycle than clomiphene with a lower risk of multiples and, in particular, higher-order multiples (triplets or greater).[11,12]

Although clomiphene citrate has traditionally been a reasonable first-line option for people with anovulatory infertility, this practice is considered outdated by most of the fertility community. Arguably, clomiphene should only be used with close monitoring of follicular size and number together with estradiol level to accurately assess risk of multiples and risk of adverse side effects (including OHSS). For primary care providers with access to fertility services, there is no compelling reason to use clomiphene without close monitoring for safety in the community. For physicians without reasonable access to fertility services, it would be advisable to have a thorough discussion with patients about the risks and benefits of clomiphene as well as letrozole before initiating either medication. For those patients who insist on trying clomiphene, documentation of risks, side effects, and recommendations for selective reduction of higher-order multiples should be made. Patients should be counseled that the use of letrozole is off label, but so are many treatments and this alone is not reason enough to not use the medication. Patients should be made aware of the increased pregnancy rate, lower risk of multiples and higher-order multiples, and lower risk of intrauterine growth restriction with letrozole compared with clomiphene. Patients should always be seen and have a documented negative pregnancy test before initiating a subsequent cycle of either medication to prevent accidental use of either medication in pregnancy.

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Competing interests
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