Quintuplets: A Rare Event Following Clomiphene Citrate Therapy

To the Editor:

We read with great interest the case of quintuplets following clomiphene citrate therapy reported by Tallon and Case, and we would like to comment regarding the current use of clomiphene citrate in unexplained infertility.

While the effectiveness of clomiphene citrate in the treatment of oligo-ovulatory women has been demonstrated, its use in unexplained infertility remains controversial. In fact, expectant management, controlled ovarian stimulation plus intrauterine insemination and in vitro fertilization are among the possible treatments options for unexplained infertility. According to the most recent Cochrane review, clomiphene citrate was found to be no more effective than no treatment or placebo for clinical pregnancy or live birth, independent of the use of intrauterine insemination or human chorionic gonadotropin. Clomiphene citrate increases the number of follicles produced per cycle and, therefore, increases the number of potential oocytes to be fertilized. Hence, ovulation induction with clomiphene citrate in unexplained infertility, which by definition includes women with ovulatory cycles, must be done very carefully because it can easily lead to multiple ovulations and multiple pregnancies. Moreover, with no clear positive impact on the live birth rate, clomiphene citrate can definitely be considered as risky, as shown in this Image of the Month.

Furthermore, we would like to emphasize the need for close ultrasound monitoring of the follicular response when clomiphene citrate is used in conjunction with gonadotropins. In the case mentioned, human chorionic gonadotropin was used to trigger ovulation, which most probably led to the fertilization of five oocytes. Most high order pregnancies could be averted with ultrasound monitoring which could, if needed, prompt cancellation of the cycle or conversion to rescue IVF.3

On the other hand, we understand that access to some fertility treatments, such as IVF, is limited because of their high cost, and many physicians and couples would consider less expensive alternatives such as ovulation induction with clomiphene citrate. However, the contribution of ovulation induction to high order multiple births is rising, while the number of multiple births from IVF is falling.3 For this reason, we believe that general public access to IVF treatments across Canada could be beneficial in the prevention of multiple births and their consequences. Furthermore, the cost-effectiveness of publicly funded IVF with elective single embryo transfer programs has been demonstrated, and Quebec’s recent program giving IVF access to subfertile couples has already shown a positive impact on the rate of multiple gestations.

In summary, there is no clear evidence that clomiphene citrate has any clinical benefit for unexplained infertility. When this treatment choice is made, the potential side effects, risks, and complications should be clearly discussed and carefully monitored for, to ensure they are reduced as much as possible.

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In Response

To the Editor:

We thank Dr Bergeron and colleagues for their thoughtful comments regarding the case presented in the March “Image of the Month.” We agree with many of them, and we are currently finalizing a more detailed case report that highlights many of the points discussed.
Unexplained infertility remains one of the most frustrating infertility diagnoses, for both patients and physicians. Without the benefit of a specific diagnosis, patients are offered empiric treatments, which include controlled ovarian hyperstimulation (COH) to produce multiple follicles in an effort to increase monthly fecundity. Therein lies the risk of multiple pregnancy, 10- to 20-fold above the natural rate (7.5% to 29%).

The alternative to COH is IVF, the most successful fertility treatment. The risk of multiple pregnancy with IVF is 30.2%, with a high-order multiple birth rate of 1.1%, related in both cases to the number of embryos replaced. Only in Quebec, with the application of an elective single embryo transfer policy for a total of three IVF cycles, do we see the risk decreased to 5.2% with a concomitant acceptable pregnancy rate. For the vast majority of couples, IVF is not funded and may be financially out of reach. Moreover, IVF may not be acceptable to all patients because of the associated ethical, financial and emotional costs. Consequently, other avenues of treatment such as COH with clomiphene or gonadotropins are discussed. We agree that general public access to IVF treatments across Canada could be beneficial in the prevention of multiple births and their consequences.

This case led to a reconsideration of practice in our clinic. Patients are carefully counselled about options for treatment of unexplained infertility. While IVF is definitely the most successful treatment, the cost of treatment is considerable and often factors significantly in decision-making. While we, and our patient, are thankful for the ultimately very positive outcome, we recognize the burden of risk that resulted from the treatment provided. This has reinforced the importance of having up-front frank discussions with patients about risks of multiple pregnancy, and cycle cancellation in the event of a multifolllicular response.

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Delayed Laparoscopic Management of Placenta Increta

To the Editor:

I read with interest the article “Delayed laparoscopic management of placenta increta” by Arendas et al.1 Repeat Caesarean section (CS) was performed for placenta increta with the placenta left in situ. Although delayed laparoscopic hysterecotomy had been planned, it was performed earlier because of infection. Although the presence of placenta previa in this patient is unclear, let us assume that she had placenta previa, and the term placenta “accreta” (accreta, increta, and percreta) will be used here for brevity. In short, placenta previa accreta (PPA) was successfully treated by delayed laparoscopic hysterecotomy, although it was performed earlier than planned. Thus, this case consisted of two steps: delayed hysterectomy and then laparoscopic surgery. In each step, I have some concerns.

As to the first step, I am interested in the authors’ fundamental strategy to deal with PPA. Do they recommend “delayed hysterectomy”? Generally speaking, there are three strategies for PPA: (1) Caesarean hysterectomy, (2) planned delayed hysterectomy, and (3) a “conserving” strategy (waiting for spontaneous absorption or separation of the placenta). A recent article in this Journal2 illustrates the third strategy well. There is another strategy: (4) “palliative CS only” when there is no alternative to CS at the time. For example, this would apply with placental invasion to the parametrium or with nighttime surgery, in which case Caesarean hysterectomy may threaten the mother’s life. The report by Arendas et al.1 described the merits and demerits mainly of strategies (1) and (3). Would the authors wish to comment on the superiority of strategy (2) to the others?

As to the second step, the authors employed laparoscopic hysterectomy; however, its superiority to open hysterectomy is not clearly described. I understand that laparoscopic
hysterectomy, if performed by experienced surgeons, may be less invasive than open surgery. Does this hold true also for postpartum hysterectomy? I recently described the hidden danger of “conserving” management of PPA in this Journal. In short, a “conserving” strategy frequently requires emergency peripartum hysterectomy, which is dangerous because a multi-disciplinary team is difficult to assemble at night. I believe that this also holds true for a delayed hysterectomy strategy and even more so for laparoscopic hysterectomy. Arendas et al. concluded that “Key factors for success consist of (1) a multi-disciplinary approach, (2) the availability of skilled laparoscopic surgeons, (3) advanced endoscopic equipment, and (4) the availability of resources (including blood transfusion).” In many institutions, all four of these are quite difficult to obtain for emergency surgery at night.

Peripartum hysterectomy requires many measures different from routine hysterectomy. I myself devised various measures, some of which were briefly described in this Journal. We must also consider the rarity of Caesarean hysterectomy due to placenta accreta. In the Placenta Clinic at Mount Sinai Hospital in Toronto, with a catchment area of 80,000 deliveries per annum, 68 patients had placenta accreta to the extent that Caesarean hysterectomy might be required during a 10-year period, indicating that Caesarean hysterectomy for this condition may be performed in approximately 1/10,000 deliveries. Since peripartum hysterectomy requires some different measures and since this surgery may be performed only rarely, a long time may be required for surgeons to become accustomed to performing laparoscopic peripartum hysterectomy and the number of patients benefiting from it may be small.

Arendas et al. concluded that “a laparoscopic approach may be considered for delayed surgical management of abnormal placentation.” Of course, a laparoscopic approach may be considered, depending on the situation of the institution. However, the number one priority is to identify which strategy (Caesarean hysterectomy, delayed hysterectomy, or conserving management) is the best. Discussion of laparoscopic versus open surgery is the next step. While doing so, it is important to consider that at many institutions, even in developed countries, nighttime surgery is a challenging situation. Thus, although I applaud the authors’ pioneering effort, I believe that it may be too early or even dangerous to generally employ delayed laparoscopic hysterectomy in women with PPA.

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In Response

To the Editor:

We would like to thank Professor Matsubara for his interest in our case report describing a delayed hysterectomy for placenta increta. In addition, we appreciate this important dialogue, which also includes his previous comments regarding the risks of delayed hysterectomy.

With respect to the specific questions regarding our case report, we would like to clarify a few issues:

1. There was no placenta previa in this case. As noted in our article, we were dealing with an invasive placenta (increta) only.

2. The initial plan in this patient’s care was actually a planned Caesarean hysterectomy. However, the patient came in on a weekend, and our colleagues elected to leave the uterus with the placenta attached to minimize the risk to the patient. As Professor Matsubara mentions, hysterectomy in these cases requires experienced surgeons and staff, ideally during a weekday when all hospital resources may be accessed. This was not the case at the time this patient presented. The risk of performing a hysterectomy at the time of Caesarean was felt to be unsafe and unpredictable. I applaud my colleagues for moving forward with this option. Often surgeons feel compelled to work outside their comfort level or surgical expertise, but in this case they made a wise and safe decision.

3. A delayed hysterectomy was planned in order to safely remove the uterus after six weeks to allow for maternal recovery and involution of the pregnant uterus. The patient was followed closely and the earlier laparoscopic hysterectomy was done when the patient presented with mild symptoms to avoid more complicated outcomes (e.g., sepsis, hemorrhage).

4. At our institution, for the last three years, we have had a surgical obstetrics team that deals with complex...
invasive placental cases. Team conferences including our experts in surgical gynaecology, anaesthesia, and referral services (e.g., urology, general surgery) meet to discuss the cases in advance in order to plan the surgical approach in advance. Back-up plans are also discussed in case the “team” is not able to mobilize after normal working hours. This has allowed a few surgeons from our department to gain greater experience with these cases.

Lastly, we do not apologize for showcasing a laparoscopic approach. Laparoscopy is simply a method of entry. Once inside the abdomen, the surgical principles we follow are similar to the open approach. The improved visualization and ability to provide dissection with minimal blood loss are the advantage of laparoscopy in expert hands.

We acknowledge that laparoscopy may not be available in all centres. We respect that the skills necessary to perform this type of hysterectomy are not widely practised. However, the expertise and equipment at our centre allow us to provide this type of approach, and we are not alone (as shown in a previous publication).

The context of our current practice is important. At our institution we have a tertiary level gynaecologic surgery referral service. Difficult benign hysterectomy cases are sent to a group of surgeons who provide expertise that has come from fellowship training and high volume exposure. In our practice, we have a 94% minimally invasive hysterectomy rate for difficult cases, including obese patients, larger uteri, and severe endometriosis including bowel and ureteric involvement. With that as our reference, this total laparoscopic hysterectomy was not out of the ordinary in terms of the complexity we handle on a daily basis.

In summary, we respect Professor Matsubara’s comments and contribution and agree with his approach of planned Caesarean hysterectomy to reduce morbidity in expert hands. However, each case is individualized, each surgeon’s approach is based on his or her skill set, and the plan may change according to the patient’s circumstances. While we would have ideally performed a Caesarean hysterectomy at the initial presentation, the procedure was delayed in the best interests of the patient. When the patient presented, all the individuals and equipment were available to provide the patient with the least invasive approach.

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