

Excerpts From the World Medical Literature



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Goldberg HR, McCaffrey C, Amjad H, et al. Fertility and pregnancy outcomes after robotic-assisted laparoscopic myomectomy in a Canadian cohort. *J Minim Invasive Gynecol* 2022;29:72–6.

Summary: This is a single-centre, retrospective case series to determine the pregnancy rate in patients trying to conceive after robotic-assisted laparoscopic myomectomy (RALM). Secondary outcomes included whether patients underwent fertility treatment, the live birth and spontaneous abortion rates, and obstetrical complications. A total of 123 patients underwent RALM between 2008 and 2015, of whom 101 consented to be interviewed. The average age at the time of surgery was 34.4 years, and median body mass index (BMI) was 25.2 kg/m². Average myoma size was 8.9 cm; the median number of myomas on preoperative imaging was 1.0, and 98% of these were either intramural or subserosal. Seventy percent of patients were symptomatic (bleeding and bulk symptoms), and 30% presented with fertility issues. All procedures were performed using the same technique with the da Vinci robot. Adhesion barriers were not used routinely. After RALM, 60 of the 101 patients attempted pregnancy, and 70% (42 of 60) became pregnant. Those who became pregnant were significantly younger (33.7 vs. 36.4 years; $P = 0.015$); otherwise, there were no differences with respect to myoma size, myoma location, BMI, history of infertility, or use of assistive reproductive technologies. Sixty-one percent of the patients who had seen a fertility specialist before surgery (11 of 18) conceived, eight of whom conceived with the help of assistive reproductive technologies and only three (27.2%) of whom did so without it. All patients who delivered after RALM had cesarean deliveries; the rate of preterm birth was low (4 of 38 patients), and 15% miscarried. Twenty percent of patients continued to experience bleeding or bulk symptoms after surgery.

Comment: The paper and the accompanying editorial caught my attention because of its Canadian authorship and review by Tomasso Falcone, who was at McGill before his successful career at the Cleveland Clinic. I do not perform RALM or robotic surgery and, in fact, do very few laparoscopic myomectomies because my typical patient has neither a single fibroid nor a BMI of ~ 25 kg/m². Now that that is out of the way, the authors are to be commended for their good results and long-term follow-up of what must be the largest Canadian RALM cohort. It is reassuring that they had a very good pregnancy rate with few adverse obstetrical outcomes; a rate of preterm birth comparable to the “average” and a low rate of pregnancy loss without a single case of uterine rupture (although none of these patients laboured). As the accompanying editorial points out, these patients had symptoms rather than infertility as the primary indication for surgery, and only 2% had submucosal fibroids (where the association between fibroids and infertility is likely greatest). There is also little evidence that the use of the robot has benefit with respect to pregnancy outcomes; the benefit is primarily surgeon ergonomics, which cannot be discounted. The literature on more complex RALM—multiple fibroids of comparable or larger size—shows these surgeries to be very time consuming; I have reservations about the use of limited operating room time in our Canadian context and its impact on wait times, although I understand those who would argue the benefit of easier recovery justifies the cost and time.

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Serres-Cousine O, Kuijper FM, Curis E, et al. Clinical investigation of fertility after uterine artery embolization. *Am J Obstet Gynecol* 2021;225:403.e1–22.

Summary: This was a retrospective cohort study of 398 patients under the age of 43 years who were treated by uterine artery embolization (UAE) for symptomatic uterine fibroids (UFs) and/or adenomyosis between 2003 and 2017, performed by a single physician in two private hospital centres. The primary objective was to study clinical, anatomic, and obstetrical outcomes in patients of reproductive age “not eligible for myomectomy.” Indications for the procedure included the presence of a single fibroid >5 cm, multiple fibroids and/or adenomyosis, and age <43 years. Desire for fertility preservation was *not* an exclusion criterion. Of 676 eligible patients, 398 available for follow-up were included in the study. Extensive pre-embolization data were collected, including demographics (e.g., age, parity, symptoms, use of in vitro fertilization). Postembolization data included symptoms, recurrence, need for surgery, live birth, miscarriage, and abortion. All patients had pre- and postprocedure magnetic resonance imaging scans at 3 months, followed by ultrasound every 3 months for 1 year after UAE. A “fertility-sparing” technique was used, which involved placement of microcoils in any significant utero-ovarian anastomoses identified on initial angiography. Logistic regression analysis was used to determine predictors of clinical and obstetrical success. Mean age was 37 years; 161 (43.4%) were parous, and 158 (39.7%) wished to become pregnant. Three hundred forty-seven of 363 patients (95.6%) had a distorted uterine cavity. Most patients in this series had a *solitary* myoma; 20% had two, and only 18% had multiple UFs. Clinical success, as defined by improvement in bleeding or bulk symptoms, was observed in 91% of patients. The main predictors of clinical success were low number of fibroids and restoration of normal anatomy ($P < 0.0001$). Very few patients required subsequent surgery. With respect to obstetrical outcome, there were 148 pregnancies in this cohort, of which only 11 required in vitro fertilization. There were 109 live births (73.7% of all pregnancies), and a miscarriage rate of 17.6%. The rate of preterm birth was 23.4%, and remarkably there was only one case of placenta previa and one adherent placenta. Predictive factors for favourable obstetrical outcome also included restoration of normal anatomy (odds ratio 7.3×10^8) and ovarian protection (odds ratio 13.65; $P = 0.001$); these results remained significant after adjusting for age at the time of UAE.

Comment: Lots of data to digest here—the full paper runs to 22 pages with supplemental charts. Like the preceding

study, this was a population of *symptomatic* and not necessarily *infertile* patients; this limits the validity of pregnancy as an outcome, to some extent. However, this series is quite impressive for the depth and detail of the demographic, technical, imaging, and outcome data. The reason I have chosen to review it is that I have always been intrigued by the stark difference in attitude between French and North American gynaecologists in considering UAE for symptomatic patients with UFs who wish to preserve fertility because of the concerns about iatrogenic ovarian failure (1%–2%) and adverse pregnancy outcomes. UAE was developed in France by Ravina in the early 1990s, so it is no surprise they may be more enthusiastic and avant-garde than we are. My immediate reaction was “Does this represent the patients I see every day?” In this case, not really. Most patients in this study had one or two UFs, and only 20% had multiple UFs; most of the challenging patients I see have large and multiple UFs, and UAE is being considered as an alternative to a potentially more morbid myomectomy. The inclusion of patients with adenomyosis was also surprising given the generally disappointing results of UAE in these patients. The pregnancy outcomes in this cohort are quite reassuring, with very few of the adverse outcomes we have feared—growth restriction, antepartum bleeding, and abnormal placentation. The “fertility sparing” technique described here may not be performed by all interventional radiologists, but this paper will encourage me to have a dialogue with our radiologists and consider more liberal uptake of UAE in patients who may be at high risk for adverse surgical outcomes.

Mehdizadeh Kashi A, Niakan G, Ebrahimpour M, et al. A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. *Int J Gynaecol Obstet* 2022;156:124–32.

Summary: This was randomized, double-blind pilot study that included 108 women in Iran who had severe endometriosis confirmed by laparoscopy. The primary objective was to compare the efficacy of dienogest (DNG) (Visanne, Bayer) and the combined oral contraceptive (COC) pill on pain and quality of life (QoL) in these patients when given postoperatively. Inclusion criteria included age 18–45 years, BMI 18.5–29.9 kg/m², subjective symptoms during menses (dysmenorrhea, dyspareunia, dyschezia), and stage IV disease confirmed by laparoscopy. Patients had excision of disease, including bowel and ureteral implants. Medical treatment was initiated 1 week after surgery. Patients were randomly assigned

to DNG, a 30 µg oral contraceptive with 300 µg of levonorgestrel, or placebo. Patients were treated for 6 months. The primary outcome was change in pain scores as measured on a 10-point visual analogue scale. Secondary outcomes included effects on QoL scores as measured by the World Health Organization Quality of Life Instrument, short form (WHOQOL-BREF), a scale containing 24 items divided into four domains: physical, psychological, social, and environmental. Of 126 eligible patients, 108 were included in this analysis; equal numbers from each of the three groups dropped out before the end of the 6-month period. All three groups were equally matched for all demographic factors (age, parity, BMI, infertility). Mean pelvic pain scores decreased in the DNG, COC, and placebo groups by 5.39, 5.79, and 3.14, respectively, from baseline to 6 months. A significant difference was noted between the DNG, COC, and placebo groups ($P < 0.001$), but there was no significant difference between the two intervention groups. For dyspareunia, significant differences were also seen between the DNG, COC, and placebo groups (mean difference -2.14 , -2.86 , and -0.48 , respectively; $P = 0.040$). For the secondary outcomes, mean difference in QoL was 22.00 and 23.45 in the DNG and COC groups ($P < 0.001$ for both) and only 6.45 in the placebo group ($P = 0.004$). No significant difference was seen between the two intervention groups. Adverse events and discontinuation rates were low (2.8%). The authors note that this was the first randomized, double-blind, placebo-controlled trial comparing the effects of DNG and COCs on pelvic pain and QoL in women with endometriosis.

Comment: My initial reaction: “No one has looked at this before? You have to be kidding!” Gynaecologists have adopted the “off-label use” of COCs as a convenient, effective, and familiar option to treat endometriosis for over 30 years. When DNG appeared on the scene over 15 years ago, it filled an “unmet need”: an effective, cheap, tolerable, oral option, as effective as the “gold-standard” GNRH agonists. The COC pill is generally prescribed for sexually active women without contraindications to estrogen, and DNG for patients who do not need contraception or cannot tolerate COCs. Picking one or the other depends on patient and provider preference, and there is certainly some overlap between the two. This well-designed, albeit small, study with a short follow-up period clearly demonstrates the efficacy of both options with minimal differences with respect to pain relief and overall QoL. (Interestingly, neither drug showed benefits in dyschezia or dysuria.) Other papers have demonstrated lower risk of recurrent endometrioma after surgery with COCs, but no other studies have compared these two

options head-to-head with placebo. The discontinuation rate seemed surprisingly low to me; my own experience is that a higher number of patients will abandon treatment with DNG, despite almost complete pain relief, because of abnormal bleeding. With the advent of GNRH antagonists, someone out there should consider a similar trial comparing them with COCs. Now *that* would be interesting...

Younis JS, Shapso N, Ben-Sira Y, et al. Endometrioma surgery—a systematic review and meta-analysis of the effect on antral follicle count and anti-Müllerian hormone. Am J Obstet Gynecol 2022;226:33–51.e7.

Summary: This was a review and meta-analysis of 14 prospectively designed studies performed between 2000 and 2020 that evaluated the effects of endometriotic stripping ovarian cystectomy on antimüllerian hormone (AMH) levels and antral follicle counts (AFC) in the same women at matching time points in the same setting. This paper analyses the results of 650 women from studies performed primarily in non-Western countries. The largest single study was from Iran and included close to 400 women; other studies ranged from 10 to 120 patients. One hundred fifty-seven of 650 women had undergone unilateral cystectomy, and all others had undergone bilateral cystectomy. A stripping technique with bipolar cautery for hemostasis was an inclusion criterion for eligibility. All patients had early (1–6 weeks), intermediate (2–6 months), and late (9–18 months) measurement of AMH and AFC. All included studies were assessed as having a low risk of bias. The postoperative weighted mean difference of AMH dropped by 1.77 ng/mL at 6 weeks (95% confidence interval [CI] 0.77–2.77; $P < 0.001$), 1.17 ng/mL at 2–6 months (95% CI 0.66–1.67; $P < 0.001$), and 2.13 ng/mL at 9–18 months (95% CI 1.61–2.65; $P < 0.001$); this represents a mean reduction at each of these time points of 44.1%, 35.1%, and 54.2%, respectively. The AFC did not change significantly at any of these time points: the early AFC was 0.70 (95% CI -2.71 to 3.56; $P = 0.63$), intermediate count was -0.94 (95% CI -2.53 to 0.65; $P = 0.25$), and late count was 2.58 (95% CI -0.43 to 5.58; $P = 0.09$); this represents a change of +10.3%, -10.1% , and +34.1% at these respective time points. There were high levels of heterogeneity for both AMH and AFC, likely related to the differences in laboratory assays and imaging technique. In the subgroup analysis of women with *unilateral* cystectomy, there were no significant differences in AMH or AFC at any of the time points. AFC was unchanged in *both* the operated ovary and the contralateral ovary. The authors conclude that AMH is a

more sensitive biomarker of damage to the ovary than AFC, and this information should be used to guide counselling for surgery in patients with infertility.

Comment: First impression: “Is this information relevant, and will it change my practice?” This is a well-done study, notable for its rigorous inclusion criteria with plenty of data, evaluation for bias and heterogeneity, and even a deep dive into the actual assays used to measure AMH in this international study. On the surface, sounds pretty good. However, we are looking to base conclusions to change practice on data from 650 patients, almost two-thirds of whom were from one study (from Iran). Moreover, a minority of patients had unilateral endometriomas. Most of the patients I see have unilateral endometriomas; this may reflect my practice as a generalist rather than an “endometriosis specialist” or REI. There is no doubt we have all been sensitized to the fact that the residual ovary sustains

significant collateral damage when we “strip” these cysts; that has encouraged us to be more conservative in managing smaller endometriomas in asymptomatic patients when there is no clear evidence of infertility and to consider medical management for a condition that was once an “absolute indication” for surgery. Although the evidence is clear from this paper that AMH is affected consistently and temporally despite maintenance of normal numbers of follicles, the question remains whether this ultimately has an impact on fertility in such patients. In 6 of the 14 studies included, the indication for surgery was not recorded, and there is no long-term follow-up on pregnancy rates in these women. My takeaway is to remain thoughtful and conservative when performing surgery for endometriomas and to consider alternative techniques such as fenestration, use of vasopressin to limit bleeding, or laser vaporization when surgery is necessary. Evolving data on the use of medical management are also slowly changing practice.