



FERTILITY AND DELIVERY AFTER ILEAL POUCH ANAL ANASTOMOSIS

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Introduction

Restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) has become the gold standard surgical treatment for mucosal ulcerative colitis (UC) and familial adenomatous polyposis (FAP) syndrome patients. IPAA in UC avoids a permanent stoma and provides an increased quality of life and in FAP patients, IPAA has the advantage of removing the entire at-risk colorectal mucosal surface. Due to the fact that these conditions both have an early onset, surgical treatment is commonly performed during the reproductive years.

This fact is of great concern, since it has been suggested that surgery has a negative impact on the ability to conceive children. The aim of this paper is to review the pertinent literature concerning infertility after IPAA, with an emphasis on etiological factors and mechanisms of infertility, various prevention strategies and potential treatments. The controversial topic of vaginal versus cesarean section (C-section) delivery after IPAA construction will also be addressed.

Infertility after IPAA

A large number of women who have undergone IPAA for either UC or FAP are young and have not started or completed their families, which is an important fact, since up to one half of patients wish to conceive after surgery [1-2]. A variety of studies, many using different measures of fertility, have consistently shown that IPAA has a significant negative impact on a female fertility [1-6]. Two early studies from Scandinavia demonstrated a 36% chance of becoming pregnant after IPAA compared to 88% of females in the general population and 90% of females with UC who have not undergone surgery [7]. The same authors also looked at fecundability (the biological ability to become pregnant per month of unprotected intercourse) and

found an 80% decrease. Furthermore, it was found that 29% of females who did end up conceiving, required in-vitro fertilization [5]. A study from Johnson, et al in 2004 reviewed pre- and post IPAA fertility rates (defining infertility as the inability to become pregnant after 12 months of unprotected intercourse). The authors found a 36.8% infertility rate in surgical patients compared to 13.3% in the non-surgical patients. They also reported that fertility treatment was significantly higher in the post-IPAA group (30%) versus non-surgical group (3%) [2]. Similarly, in a study from our institution, Gorgun and colleagues reviewed 300 patients retrospectively and found an increase in infertility after IPAA for UC and FAP. Pre-IPAA, 38% of



patients were unsuccessful in achieving pregnancy after 1 year of unprotected intercourse versus 56% of patients post-IPAA [1]. The study also demonstrated that females between the ages of 30-39 exhibited the highest infertility rate post-IPAA. A recent meta-analysis by Rajaratnam and colleagues, demonstrated a statistically significant increased relative risk of infertility of 3.91([2.06, 7.44] 95% CI) post IPAA. This meta-analysis reviewed key papers that documented both pre- and post-IPAA infertility rates. The authors noted average infertility rates of 20% pre- and 63% post-IPAA [8]. This data is similar to an older meta-analysis by Waljee and colleagues, which showed a relative risk of infertility at 3.17 and pre-IPAA (medically-treated UC) infertility of 15% and post-IPAA of 48% [9]. Most of the studies on infertility related to IPAA are extremely heterogeneous and differ in their methodology. This makes them difficult to interpret at times and also makes comparing various studies impossible. All studies involve retrospective interviews or

questionnaires which have a potential for recall bias. There also is a lack of a standardized definition of what infertility truly is. Infertility is defined as inability to conceive after one year unprotected intercourse, but few studies use this definition. This definition also does not include women who got pregnant after 12 months, as highlighted by Lepisto and colleagues, in which the authors showed that fertility rates after six years post-IPAA increased to 76% [10]. The use of fertility treatment may also skew results as enrollment into a fertility program, which by definition, does not allow for natural pregnancy to occur, thus falsely decreasing rates of achieving pregnancy. It should also be mentioned that many published studies have used the same population of women pre-IPAA as their own control group for post-IPAA patients. Using the same women as their own controls is troublesome, as it has been shown that with aging, women have increased fertility problems, regardless of surgical intervention undertaken [8].

Potential Mechanisms of Infertility after IPAA

Anatomical derangement, including adhesions and scarring with subsequent tubal abnormalities is considered the most likely cause for infertility after IPAA [8]. Pelvic adhesions after proctectomy distort the normal anatomic relationship between the ovaries and the fallopian tubes, likely preventing ovum capture [1]. It does not matter if a pouch is created after the proctectomy as infertility rates are similar in women with a proctectomy only [11].

Investigating the concept that tubal adhesions are likely responsible for

infertility after pelvic dissection, Oresland and colleagues performed hysterosalpingography (HSG) in 21 patients post-IPAA and found that only 7 patients had normal anatomy. Fifty-two percent of the patients had at least unilateral tubal occlusion of the fallopian tubes and in 48% of patients, the tubes were adhered to the pelvic floor [4]. A limitation to this study is that that HSG was not performed pre-IPAA. Similarly, in another study from the same institution, Asztely et al showed that on vaginography and HSG, 57% of women had



tubal occlusion and 95% had tubal adherence to the pelvic floor [12]. Likewise, Cornish and colleagues published, in abstract form, a review of IPAA patients that were infertile and found that tubal factors were responsible for infertility in 80% of patients as compared to 30% of controls [13]. There may also exist other mechanisms of infertility besides anatomical factors from pelvic adhesions. Sexual dysfunction from dyspareunia, vaginal factors, such as dryness, and the fear of

incontinence, coupled with a potential negative body image, may also play a role in the high rate rates of infertility in post-IPAA females. In the FAP population, the unique psychological fear of potentially passing on a genetic mutation to their offspring may also play a role. This concern was reported in up to 23% of patients in a study by Olsen and colleagues [6]. Lastly, a fear of the potential effects of pregnancy and delivery on pouch function may also precipitate higher infertility rates in post-IPAA patients.

Risk Factors

In the study from our institution by Gorgun et al, several variables were examined as potential risk factors for infertility after pouch surgery. The variables that were examined in patients trying to conceive both pre and post-IPAA (n=56), included: history of prior colectomy, proximal diversion, pouch type (J versus S), oophoropexy, adhesiolysis, use of anti-adhesion barriers, and intraoperative blood transfusion. The only significant finding associated with infertility was intraoperatively the need for a blood transfusion (p=0.023) [1]. The authors concluded that the need for transfusion was a marker of more difficult

surgery and infertility was unlikely from the blood transfusion itself.

In another study of infertility post-IPAA, Johnson and coworkers found increasing age to be a significant risk factor for infertility after pouch surgery [2]. However, as women get older they can have problems with fertility as mentioned above (using women themselves as their own controls before and after surgery). Therefore, this study may only confirm what is known—namely age itself is a risk factor for all women in general.

Prevention Strategies and Treatment

With the apparent increase in infertility after IPAA, several potential preventative tactics to help reduce or minimize the risk of infertility have been proposed. An emphasis on preoperative strategies, intraoperative

maneuvers, and postoperative options is included. It should be noted that none of these techniques have been prospectively proven to decrease infertility rates in post-IPAA patients.



Preoperative Considerations

Preoperative strategies involve both the type and timing of surgery for UC and FAP patients. This is especially true in younger patients who have not yet completed their families. Since adhesions from pelvic dissection are the leading factor for infertility, the option of rectal preservation could be considered whenever rectal involvement is minimal. Although rectal preservation may not always be feasible in UC patients due to disease characteristics, some centers advocate ileorectal anastomosis (IRA) in selected cases where fertility may be an issue [14]. Mortier and colleagues looked at IRA in 15 patients and found a relatively low infertility rate of 33% after surgery. Another potential option for rectal preservation includes performing a subtotal colectomy with end ileostomy as a first stage procedure in young females with UC and then delaying the IPAA until after their family is complete. While these options of leaving the rectum behind have the potential advantage of decreasing pelvic adhesions, risks of leaving an inflamed rectum must be considered. Additionally, it is hard to imagine a young woman (who may be body conscious and not yet married) to accept an ileostomy over a pelvic pouch. They typically are traumatized enough with their disease and the need for surgery and the thought of a stoma for one minute longer than absolutely necessary is inconceivable.

Dr. Victor Fazio (who is the past chairman at our institution) has said that when he presented these two alternatives with the benefit of an ileostomy being potentially improved fertility, the mothers frequently would encourage their daughter toward ileostomy, while the patient uniformly chose a pelvic pouch! (personal communication with Dr. Victor Fazio).

FAP patients pose a more challenging dilemma for potential rectal preservation secondary to an increased risk of rectal cancer. Even though an IRA may provide superior function and potentially improve fertility, it may expose the patient to an unacceptable high risk of developing rectal carcinoma. This risk is especially concerning in patients with severe polyposis, a mutation at codon 1309 of the Adenomatous Polyposis Coli (APC) gene, and those patients over 25 years old. This particular patient population may need to avoid rectal preservation and be definitively treated with IPAA [15-16]. However, it should be noted that the long-term risk of developing a malignancy in the pelvic pouch is not definitively known and may not be insignificant [17]. Therefore in select patients with few rectal polyps that can all be removed prior to surgery AND those who are reliable and will return to be surveyed with a flexible sigmoidoscopy on a frequent basis, an IRA can be considered.



Postoperative Considerations

Postoperatively after an IPAA, early referral to a fertility specialist should be strongly considered for all patients who wish to conceive. Few publications exist regarding post-IPAA in-vitro fertilization (IVF). A study from Finland reported success in 8 of 12 patients post-IPAA with fertility treatment methods [10]. Further research is required to determine the success of fertility treatments after IPAA.

Intraoperative Considerations

Oophoropexy and omental pedicle interposition

The technique of suturing both ovaries to the pelvic sidewall/brim has been advocated to prevent entrapment of the ovary behind (or beside) the pelvic pouch. In Gorgun and colleagues study, oophoropexy did not correlate with any preservation of fertility [1]. However, oophoropexy may prevent “entrapped ovary syndrome,” which may predispose the patient to chronic pelvic pain and ovarian cysts in the future [20]. One potential down side of oophoropexy may be difficulty in accessing the ovaries via the

Anti-adhesion products

Anti-adhesion barriers such as Seprafilm[®], Intergel[®], and others have been studied and shown in both gynecological, general, and colon and rectal surgery to decrease intra-abdominal adhesions [21-22]. The liberal use of these products to wrap the ovaries and adnexal structures at the conclusion of the surgery may be employed to potentially

Additionally, pre-IPAA patients in a stable relationship may wish to undergo embryo cryopreservation, which then may be used for IVF, if the patient was unsuccessful in conceiving naturally after surgery. Advancements in cryopreservation and ovarian transplantation may improve success rates for fertility in the future [8, 18-19].

pouch of Douglas if in-vitro fertilization methods are needed at a later time [8]. Similarly, the simple procedure of creating a greater omental pedicle graft to keep the ovaries out of the pelvis with hopes to decrease adhesions is also often used, without any randomized evidence of its efficacy. This procedure has little to no drawbacks, but it must also be considered that this procedure may increase adhesions if the omentum envelopes the ovary and tube.

decrease tubo-ovarian adhesions. Whether or not the use of anti-adhesion barriers can improve fertility after IPAA is not known at this time. In the study from our institution, the use of these products did not demonstrate any positive effect on fertility rates [1].



Laparoscopic surgery

The advantage of laparoscopic surgery for decreased adhesion formation in IPAA patients has been recently studied [23-24]. In a publication from the Mayo Clinic, Inad et al examined 34 patients that underwent laparoscopic IPAA, including 21 women. After the pouch had been constructed at the time of loop ileostomy closure, a camera was placed through the stoma aperture after bowel closure and adhesions were assessed. Few adhesions were detected in all patients, with 71% of the women having no adnexal adhesions at all. None of the women had bilateral adnexal adhesions [23]. Similarly, in a study from our institution, Hull and colleagues scored adhesions in 40 patients undergoing diagnostic laparoscopy at the time of loop ileostomy closure after both

open and laparoscopic IPAA for UC. The incisional adhesion score, the total abdominal adhesion score and the American Fertility Score (to grade adnexal adhesions) were all compared between the two groups. All adhesion scores were statistically lower after laparoscopic surgery and most of the adhesions in the laparoscopic group were at the extraction or port sites [24]. Although both these studies reported less overall adhesions and less adnexal adhesions following laparoscopic IPAA, there is no current data that proves that these decreased adhesions translate into decreased infertility post-IPAA. A prospective, multi-institutional study is needed to prove this point.

Delivery after IPAA

For women who become pregnant after IPAA, controversy exists regarding the optimal method for delivery. While pregnancy has been shown to be both safe for the mother and fetus without an increase in pouch-related complications or bowel obstructions, there is considerable fear of the potential long-term risk of fecal incontinence from occult sphincter injury or pudendal nerve damage during vaginal delivery [3, 25-27]. While it is generally accepted that pouch function deteriorates during pregnancy (including increases in fecal incontinence, daytime and nighttime stool frequency, and pad usage), it has been shown that pouch function returns to baseline after delivery [26-27]. It is the status of the sphincters and their long-term function that concerns some colorectal

surgeons. For these reasons, some surgeons and obstetricians have recommended elective cesarean section (C-section) delivery. This has increased the C-section rate for post-IPAA patients to 38%-78%, well above the North American average of 22% [28]. There are a number of studies in the literature reporting on vaginal delivery after IPAA [3, 20, 25-27, 29]. Ravid and colleagues reported on questionnaires they had mailed to 29 patients after IPAA who had 49 deliveries (25 vaginal and 24 C-section) with a 30 month follow-up. Five patients had some degree of deterioration after delivery (3 vaginal and 2 C-section). The authors found no difference comparing fecal incontinence or incontinence scores before and after pregnancy in the vaginal deliver



versus C-section versus both groups [25]. Similarly, Juhász and colleagues, with a 50 month follow up, found no statistical difference in bowel function after vaginal or C-section delivery [4]. The authors of both papers concluded that the type of delivery should be based on obstetrical considerations, with avoidance of vaginal delivery only in patients with a noncompliant, scared or rigid perineum. Alternatively, Counihan et al, recommended that the majority of post-IPAA patients should receive an elective C-section as long as the patient, surgeon and obstetrician are all in agreement [3].

Remzi and colleagues, from our institution, studied 82 women who had a delivery after IPAA. Sixty-two patients underwent C-section versus 20 who had vaginal delivery. The authors studied anal sphincter integrity with endoluminal ultrasound and also performed manometry, electromyography, and pudendal nerve terminal latency studies. After a mean follow up of 4.9 years, the vaginal delivery group had a significantly higher incidence of anterior sphincter defect (50%) versus cesarean section group (13%)

($p=0.012$). Additionally, mean squeeze pressure was significantly higher in the C-section group compared to the vaginal group. However, in this relatively short term follow-up, these differences in physiological and anatomical parameters did not statistically affect pouch function or quality of life. The authors concluded that the long-term effects of vaginal delivery are not well known and that delivery method after IPAA should not be limited to purely obstetrical dictation. Furthermore, they concluded that the recommendations for a vaginal delivery should be cautiously recommended and C-section should be strongly considered after IPAA unless there are other contraindications [29].

The literature varies widely and there is currently no set standard of care for delivery method after IPAA. Vaginal delivery appears safe in the short-term but it is unknown if the delicate balance of any impairment in the sphincter muscle and defecation pattern after IPAA is more vulnerable in the long-term. Prospective studies with a much longer follow-up will be needed to make any meaningful conclusions.

Conclusion

Patients who undergo IPAA have increased infertility compared to their preoperative state. Data on this topic is heterogeneous and there are likely some elements of publication and recall bias which may erroneously effect infertility rates in some studies. Infertility post-IPAA appears to be associated with rectal dissection and subsequent pelvic adhesions, leading to tubo-ovarian anatomical distortion and dysfunction. Rectal preservation when

feasible may be considered until the patient has completed her family in an effort to improve fertility. Early referral to a fertility specialist should be obtained for all wishing to conceive post-IPAA. For pregnant women post-IPAA, there is considerable debate regarding the optimal method of delivery. These women represent a unique population and these questions will only be answered with further research.



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