Fertility and pregnancy in patients with familial adenomatous polyposis (FAP)

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ABSTRACT

Background: Familial adenomatous polyposis (FAP) requires extensive colectomy or proctocolectomy at a relatively young age to prevent colon cancer. Many affected women may not yet have started a family and will have concerns regarding their fertility potential, the effect of surgery on fertility and what type of surgery is most suitable, as well as the likelihood of experiencing a normal pregnancy and successful delivery.

Objective: The aim of this study was to summarise the current knowledge on the fertility potential (including pregnancy and delivery) of young, female patients with FAP, before and after treatment.

Design and setting: A literature review was performed, summarising current knowledge on the fertility potential of young, female patients with FAP, before and after treatment.

Results: Contrary to what is indicated in current international guidelines, the present research revealed that women with FAP do not have a reduced chance of pregnancy before treatment, after colectomy with ileorectal anastomosis, or after proctocolectomy with ileal pouch-anal anastomosis. Pregnancy complications are not significantly increased, and vaginal delivery can be considered following careful assessment.

Conclusions: Despite only limited data being available, women with FAP can be reassured that their fertility potential is not affected by the disease. Current guidelines do not reflect the state-of-the-art knowledge on fertility and pregnancy in FAP patients and do not provide management tools to healthcare professionals. We recommend that clinicians and patients discuss the topic of fertility and pregnancy at the appropriate time before making a decision on surgery and also that further studies should be conducted, and the international guidelines amended.

KEYWORDS

Familial adenomatous polyposis; fecundity; fertility; guidance; ileal pouch-anal anastomosis; ileorectal anastomosis; proctocolectomy.

Introduction

Familial adenomatous polyposis (FAP) is an inherited genetic disease with an estimated prevalence ranging from 2.3 to 3.2 cases per 100,000 individuals. Its frequency is constant worldwide and it occurs equally in men and women [1]. FAP is caused by a germline mutation in the APC gene located on the long arm of chromosome 5 [2]. In classic FAP, patients have >100 colorectal adenomas, and the risk of developing colon cancer is nearly 100%. In such patients, it is therefore common practice to recommend prophylactic surgery. Unless there is an indication for earlier or immediate surgery, related to the overall risk of cancer posed by the polyp burden [1], the late teens to early twenties is usually considered an appropriate age for prophylactic surgery as it means that patients can have, as far as possible, a normal adolescence, with no disruption of their education, and undergo surgery at a time when it may be more socially acceptable to them [1].

The two main surgical options are colectomy with ileorectal anastomosis (IRA), for patients with limited involvement of the rectum (<20 rectal and <1,000 colonic polyps), and proctocolectomy with ileal pouch-anal anastomosis (IPAA), for patients who have severe or profuse adenomas, with high involvement of the rectum (>20 rectal and >1,000 colonic adenomas). Both surgeries are often performed via laparoscopic technique.

Young women with FAP will likely undergo a surgical operation relatively early in life, mostly prior to attempting pregnancy, and may understandably be quite concerned about whether the disease itself will have an effect on their chance of conceiving, naturally or via assisted reproductive technology; and whether there may be any detrimental effects or obstetric implications resulting from these extensive surgeries. Currently, there are very scant data available and guidelines do not address these issues. For this reason, we performed an extensive literature search to try to answer these critical questions and to determine whether more informed advice can be given to patients.

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Methods

The MEDLINE database was searched without limits on publication date or type, using the following text strings: (((((familial adenomatous polyposis OR FAP)) AND ((conception OR conceive) OR deliver* OR fecund* OR fertil* OR pregnan*))) [returning 281 publications] and ((((proctocolectomy OR (ileorectal anastomosis))) AND ((conception OR conceive) OR deliver* OR fecund* OR fertil* OR pregnan*))) [returning 141 publications]. The results were then screened manually for relevance.

Results

Fertility in patients with FAP

There are very few data on fecundity in women with FAP who have not yet undergone any surgery. This is largely explained by the young age of FAP patients at the time of surgery. We identified only three studies based on national registries — in Nordic countries [3], the Netherlands [4] and Japan [5] — that assessed fecundity before surgery [3] or after surgery [3-5] (Table 1).

In the study by Olsen et al. (2003), conducted in Sweden, Norway, Denmark and Finland, a questionnaire focusing on fertility and obstetric history, including time to conception, was sent out to all the women (N=230) in the four national FAP registers who had undergone either IRA or IPAA [3]. Of these, 162 (70%) replied and provided information on 171 pregnancies occurring prior to any operation, and 81 and 42 cases of pregnancy after IRA and IPAA, respectively. For comparison, data on reproductive health in the general population and in women with ulcerative colitis (UC) were generated from an existing database. The results demonstrated similar fecundity rates in women with FAP before surgery and after colectomy with IRA; these rates were also similar to that recorded in the general population. However, the fecundity rate dropped significantly, to 54% (p=0.015), following proctocolectomy with IPAA, albeit remaining higher than the post-operative fecundity rate of women with UC, which fell to 17% (p<0.001). Of the FAP women included in the present study, 23% chose not to conceive because of their disease. Interestingly, this was higher than the rate observed in patients with UC who underwent IPAA (16%).

No any additional published data assessing natural fertility in FAP patients were found.

In contrast, a study based on the Dutch FAP registry that addressed type of surgery, fertility potential and wish to conceive, did not find any decline in fecundity after IPAA [4]. Of the 138 patients included in that study, 23 (17%) experienced current fertility difficulties, with similar prevalence rates between those who had undergone IRA, IPAA or proctocolectomy with ileostomy. The authors concluded that the risk of developing post-operative fertility problems was not correlated to the type of surgery, its indication, complications or other comorbid conditions. They also concluded that post-operative fertility problems were more common among women who had their first surgical procedure at a younger age.

A recent Japanese FAP registry study in 80 women with information available on childbirth after surgery for FAP revealed that only 8 (10%) gave birth, after a mean time from surgery of 5.4 years [5]. This was lower than the fertility rate in the general Japanese population. However, since the study did not collect information about the patients' desire to have children, the true infertility rate following surgery could not be quantified.

In vitro fertilisation in patients with FAP

Currently, there are no studies or case reports concerning women with FAP who have undergone *in vitro* fertilisation (IVF). There are also no reports on IVF after IRA, and we identified only a single retrospective study in the USA that assessed IVF in in relation to IPAA, focusing on three groups: women who suffered from UC and had previously undergone IPAA (N=22), UC patients who did not undergo IPAA (N=49), and a control group of women without inflammatory bowel disease (N=470) [6]. The cumulative live birth rate after six cycles of IVF treatment was similar in all three groups: 64% [95% (confidence interval (CI): 44–83%], 71% (95% CI: 59–83%; p=0.63), and 53% (95% CI: 48–57%; p=0.57), respectively [6].

Pregnancy and delivery after IPAA and IRA

There are no specific studies on pregnancy and delivery in FAP patients, and all considerations made are related to the IPAA procedure and not to the disease itself. Pregnancy in FAP following IPAA is characterised by a transient increase in bowel movement frequency that subsides post-delivery. It is also not clear which is the preferred method of delivery: vaginal or caesarean section. In common practice, clinicians tend to recommend caesarean section for post-IPAA patients to prevent potential injury to the anal sphincter and to protect the long-

Table 1 Fertility in patients with FAP.

Study	Countries	Type	No. of patients	Outcomes
Olsen et al., 2003	Nordic- Denmark, Finland, Norway, Sweden	Survey of FAP register	Included: 230, responders: 162	Fecundity before surgery or after IRA is similar to that in the general population but drops to 54% after IPAA
Nieuwenhuis et al., 2010	The Netherlands	Survey of FAP register	179 females replied, 138 met the inclusion criteria	Infertility rate is similar s/p IRA and IPAA (39%)
Kobayashi et al., 2017	Japan	Data collection from FAP register	147 females, 80 with information on childbirth after surgery	8 pregnancies (10%), 5/29 (17%) after IRA, 0 after hand-sewn IPAA, and 3/20 (15%) after stapled IPAA

term functionality of the pouch, although vaginal delivery also appears to result in good outcomes [5]. A recent survey of gastroenterologists, colorectal surgeons and obstetricians found significant differences in opinions and attitudes regarding the management of delivery in post-IPAA patients, with vaginal delivery recommended by only 20% of colorectal surgeons compared with 43% of gastroenterologists, and 57% of obstetricians ($p<0.001$) [7].

Discussion

We identified only a single study, conducted in Nordic countries [3], that evaluated the fertility of FAP patients before surgery, and further two studies that dealt with pregnancy potential after surgery, either IPAA or IRA. All these studies were questionnaire based, uncontrolled and non-randomised clinical trials. It is impossible to reach any conclusions about whether natural fertility is affected by the original disease (FAP), mainly because most women undergo surgery relatively young (late teens) and may therefore not yet have attempted to get pregnant and start a family. However, the relatively small Nordic study [3] showed no reduced fecundity in these patients.

Given the limited information available in FAP patients, which we mentioned above, the effect of therapeutic/preventive surgery on fertility is derived mostly from studies in UC patients.

Those studies demonstrated no drop in fertility after IRA. Early studies following the introduction of IPAA operations in the 1980s (mostly for UC, with no or very few FAP patients) seemed to indicate decreased fertility in these patients. The hypothesis was that IPAA is performed in closer proximity to the pelvic floor, and is therefore associated with a higher possibility and risk of post-operative fallopian tube adhesion and mechanical infertility. Three meta-analyses [8-10] confirmed significant infertility prevalence post IPAA (48%, 43% and 63%, respectively). However, since the studies included in the three meta-analyses were small, retrospective in nature with biased patient selection, and lacked unified definitions of infertility, their conclusions should be treated with caution.

More recent studies have demonstrated a lower rate of fertility complications following IPAA, comparable to control group findings [11]; this may be attributed to improvements in surgical technique and procedures, and especially the introduction of laparoscopic IPAA, which results in fewer instances of adhesion formation and fallopian tube closure.

It is unclear why fecundity following IPAA surgery in women with FAP is greater than that in women with UC undergoing the same procedure. Other causes of reduced fecundity in women with FAP after IPAA may include diminished sexual health due to dyspareunia and/or faecal incontinence with intercourse. It is also possible that patients with FAP, a serious inherited disease, may refrain from starting a family for fear of passing on the polyposis gene to their children [12].

Currently there are five American/international sets of guidelines on the diagnosis and management of FAP patients (Table 2): the guidelines of the European expert group on hereditary gastrointestinal cancer [13], the European Society of Medical Oncology clinical guidelines [14], which were adopted by the American Society of Clinical Oncology [15], the Ameri-

Table 2 International guidelines and recommendations in relation to fertility and pregnancy in FAP patients.

Guideline	Organisation	Fertility recommendation	Obstetric recommendations
Guidelines for the clinical management of familial adenomatous polyposis (FAP) [13]	European expert group on hereditary gastrointestinal cancer, 2008	Studies reported that fertility was significantly reduced after IPAA compared with IRA in women with FAP. Therefore, in young women who wish to have children, an IPAA should be avoided or postponed, if possible.	None
Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines [14]	ESMO, 2013	For IPAA, more extensive surgery is needed (including pelvis dissection), causing reduction of fertility. The decision on the type of surgery depends on many factors including age, severity of polyposis (i.e. involvement of the rectum), risk of developing desmoids, the wish to have children, and the site of the mutation	None
Stoffel et al., 2015. Hereditary colorectal cancer syndromes [15]	ASCO, 2015	The decision on the type of colorectal surgery in FAP (total colectomy _ ileorectal anastomosis vs proctocolectomy _ ileal pouch anal anastomosis) depends on the age of the patient, the severity of rectal polyposis, the wish to have children, the risk of developing desmoids, and possibly the site of the mutation in the APC gene.	None
Genetic testing and management of hereditary gastrointestinal cancer syndromes [2]	ACG, 2015	Pouch surgery is associated with some loss of fertility in women	None
Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes [16]	ASCR, 2018	Factors that favour total abdominal colectomy and leaving the rectum in place include relative rectal sparing, and the desire to avoid pelvic dissection and possible infertility or sexual dysfunction	None

Abbreviations: ESMO, European Society of Medical Oncology; ASCO, American Society of Clinical Oncology; ACG, American College of Gastroenterology; ASCR, American Society of Colon and Rectal Surgeons

can College of Gastroenterology guideline [1], and the guidelines of the American Society of Colon and Rectal Surgeons [16]. All of them barely address the fertility potential of FAP patients, before or after surgery, and just mention in passing that fertility is reduced after IPAA compared with IRA, without providing any references or in-depth discussion. This finding/recommendation is not correct, since they do not take into account more recent data, described above, showing that modern IPAA procedures probably do not result in reduced fertility. None of the guidelines discuss pregnancy and delivery options, a matter very important to patients and healthcare professionals. All the guidelines recommend taking the patient's desire to have children into consideration when choosing the type of surgery, but without appropriate and accurate information, it is difficult for patients and clinicians to reach the right decision.

Moreover, we were unable to identify any study that evaluated FAP patients' concerns, fears and desires regarding their fertility and potential for motherhood, and therefore strongly suggest such studies should be conducted. All of these considerations should be included in the discussion with women who are contemplating surgery, either IRA or IPAA, so that they are well aware of them before deciding on the best management plan.

Conclusions

Despite only limited data being available, it seems that women with FAP can be reassured that their fertility potential is not affected by the disease. Many women will attempt pregnancy following proctocolectomy, and while the IRA procedure does not appear to be detrimental to conception and delivery, it is not yet clear whether IPAA results in reduced fecundity. Recent advancements in surgical techniques, in particular the introduction of laparoscopic surgery, might improve fecundity to levels similar to those recorded before surgery and in the general population, but further studies are required.

Moreover, there appear to be only minimal effects of the disease or type of surgery on pregnancy and mode of delivery, and vaginal delivery can be permitted in appropriate cases. Current international guidelines should reflect the state-of-the-art knowledge on fertility and pregnancy in FAP patients and provide appropriate information to healthcare professionals. This information, described herein, should be discussed with female patients with FAP during their treatment, especially when choosing the time and method of surgery, and pregnancy should not be discouraged.

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