

# Colorectal Cancer in Pregnant Woman

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**Abbreviations:** CRC: Colorectal Cancer; CIN: Chromosomal Instability; MSI: Microsatellite Instability; HNPCC: Hereditary Non-Polyposis Colon Cancer; FAP: Familial Adenomatous Polyposis; LS: Lynch Syndrome; PgRs: Progesterone; Ers: Estrogen; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn Disease; FOBT: Fecal Occult Blood Testing; UICC: Union for International Cancer Control

## Abstract

Colorectal cancer (CRC) is one of the most common human malignancies, affecting one of 20 persons in areas with high socio-economic standard but cases of digestive cancers during pregnancy are rare. From an etiological point of view, CRC represents an entity induced on the one hand by environmental factors and on the other hand by genetic factors or, not rarely, by their combination. The difficulty of diagnosing digestive cancers in pregnancy is the consequence of a symptomatology often masked by signs and symptoms that can be attributed to pregnancy. Essential in terms of assessing the staging of TNM in CRC, CT remains the subject of numerous debates. Over the last 40 years CT has been contraindicated in pregnant women due to teratogenic and carcinogenic effects on the fetus. Pregnancy MRI method is preferable to any other method of investigation that uses ionizing radiation. The CRC's treatment plan must take into account the interests of two people, the mother and the fetus, so that the "interest" of one does not affect the other, respecting an axiom: treatment as soon as possible for the mother after a birth as soon as possible for the fetus. Colorectal neoplasia is generally a predominantly surgical pathology at the time of disease discovery, especially in conditions of a major complication that leaves no time for a therapeutic alternative (obstruction, perforation, significant bleeding). A chemotherapy-type oncology protocol option is preferred for cases with advanced, metastatic neoplasms.

**Keywords:** Colorectal Cancer; Pregnancy; Diagnosis & Treatment

## Introduction

Cases of digestive cancers during pregnancy are rare, their reporting being sporadic. Because nowadays the pregnancy often occurs at ages between 30-39 (even between 40-49 years old), it could explain the increasing frequency association of cancers and pregnancy. Miscellaneous population trials [1-5] notes in the last 3-4 decades an explosive growth of some digestive neoplasms, especially by involving of some age groups from the fertile period of the woman between 15-49 years. By analogy with breast cancers, digestive cancers in pregnancy are defined as cancers diagnosed during pregnancy and in the first year postpartum. From the multitude of digestive visceral sites, the most frequent neoplasms appear to be the stomach, colon and rectum, only in exceptional cases liver and pancreatic cancers. Also, paraclinical evaluation of these patients is difficult, as the pregnancy trimester is an important indicator of the opportunity of a certain investigation. Precaution related to fetal involvement in the indication of invasive exploration (imaging, endoscopic, etc.) also delays the diagnosis. That is why

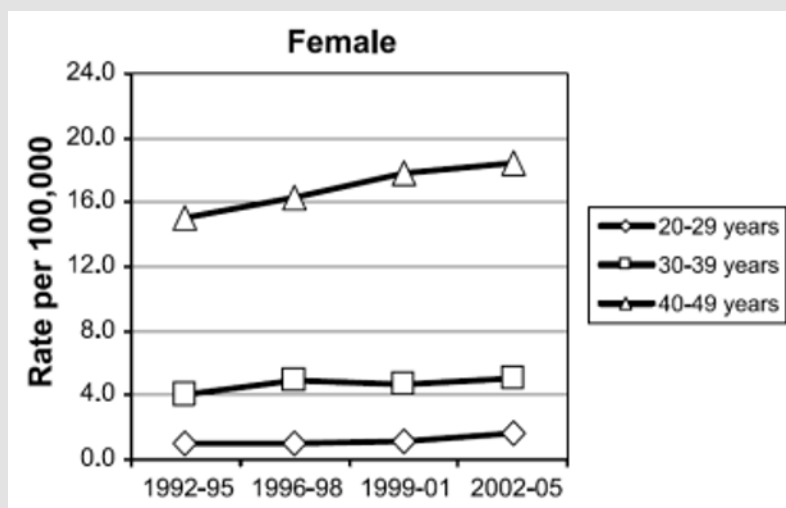
digestive cancers are diagnosed in pregnancy in advanced stages, usually in the complication phase - occlusion, hemorrhage, perforation or cachexia. The diagnostic and treatment protocols applied to the non-pregnant patient are not similar to those in pregnancy, most often a multidisciplinary approach, involving the association of medical-obstetrician-surgeon-gastro-enterologist-pediatric neonatologist-psychologist specialized in oncology, together with the patient and his family will be able to define the correct and balanced approach of the optimal therapeutic plan.

## Epidemiology

Colorectal cancer (CRC) is one of the most common neoplasms and the third leading cause of cancer death. Regarding the incidence of neoplasms in women in general, CRC ranks fourth, after breast, cervical and lung cancer. Cancer mortality in women is attributed, in order of frequency: breast, lung, colorectal and cervical cancers. Overall CRC incidence data shows a modest decrease since the 1980s in industrialized countries and a slow but steady growth in

poorly developed countries (e.g in the USA since 1998 the incidence of CRC in women has decreased by about 2.2% per year) [6,7]. This decrease is essentially attributed to the CRC screening techniques [8,9]. There was no specific incidence of CRC in pregnant women compared to that in the general population. Consequently, the incidence of CRC in fertile women is consistent with that of CRC in the general female population for decades of appropriate age

(`20-29, `30-39 and `40-49 years old) [10,11]. In the US female population covering the three decades above, it was noted that, in contradiction with the decreasing level of CRC incidence, the statistical data shows a constant growth of CRC of 1.6% per year since 1992 (Figure 1), especially among the non-Hispanic white population [12,13].



**Figure 1:** The evolution of CRC incidence in the 20-49 decades. There has been a steady annual growth since 1992 (Rebecca L. Siegel) [13].

The first 245 cases were reported between 1842-1995, and between 1996-2004 30 new cases are reported, which almost doubles the incidence of CRC in pregnant women [14-17]. In the unitary group of patients, in the three decades of age, the peak of the incidence appears in the patients of 31 years old. A particular feature of colo-rectal neoplasia in pregnant women compared to the general population is the tumor site. Thus, if in the general population the rectum comprises about 25-30% of the total CRC, in the case of pregnancy there is a counterbalance, the subperitoneal rectum being interested in most cases [18] (about 85%). This atypical behavior raises questions about the etiology of neoplasia. Firstly, a different biological behavior of CRC tumors during pregnancy is suggested. Most likely, however, the cause is the discovery of the tumor much easier at routine gynecological control during pregnancy, either due to the accentuation of the symptoms by the tumor growth together with the compression on the rectum in pregnancy.

## Etiology

### Environmental and Genetic Factors

From an etiological point of view, CRC represents an entity induced on the one hand by environmental factors and on the other hand by genetic factors or, not rarely, by their combination. From the genetic perspective, based on the causes involved in the emergence of CRC, there are three major types: sporadic CRC (60-70%), family CRC (30-40%), hereditary CRC (genetic diseases 4-6%) [19]. Sporadic CRC is rarely encountered under the age of 50.

As a result, the cases reported in literature of pregnancy associated with CRC meet the conditions of family CRC, respectively genetic. However, in sporadic CRC encountered in pregnant women, similar to the general population, we find two mechanisms of genomic instability:

- i) Chromosomal instability (CIN), consequence of alteration of genetic material, resulting in inactivation of tumor suppressor genes (ex. TP 53, APC) or activation of oncogenes (Ki-ras) in about 80-98 % of cases [20-23].
- ii) Microsatellite instability (MSI), without knowing the genes involved (10% of cases) [24,25].

Family type associates increased risk of genitors developing CRC (doubles if first-degree relatives develop CRC, especially under the age of 50), while the genetic type associates syndromes known for genetic material abnormalities: HNPCC (Hereditary Non-Polyposis Colon Cancer or Lynch syndrome), FAP (Familial Adenomatous Polyposis), AFAP (Attenuated Familial Adenomatous Polyposis), gene mutation APC1307K, Peutz-Jehger's Syndrome, MAP (MYH associated Polyposis), Juvenile Polyposis, Hereditary Polyposis. The identification of the cause that has the effect of the occurrence of the primordial-etiological mutation in the CRC is possible in less than 6% of cases [26,27]. Recent studies [27] have succeeded in characterizing and defining the malfunction of genes involved in CRC etiology in three main classes: suppressor genes (APC, AXIN2, TP53, STK11, PTEN, BMP1A, SMAD4) oncogenes (KIT, PDGFRA),

DNA repair genes (MLH1, MYH, BLM). Extremely interesting is the presence of some primary mutations as etiological induction factors for CRC, with the title of mutations, called de novo mutations. The various syndromes (FAP, JPS, Peutz-Jeghers, Cowden, Bannayan-Riley-Ruvalcaba) have high rates of de novo mutations (25-30%) [28-30], while LS (Lynch syndrome) associates de novo mutations in MMR at a reduced frequency (0,9-5%) [31-33].

**The Influences of Steroid Receptors**

The hypothesis of the involvement of progesterone (PgRs) and estrogen (Ers) receptors in CRC pathogenesis in pregnant women is extremely interesting. It was found [34-36] that at approx. 20-54% of CRC reports the presence of Ers [37-39], as other authors identify PgRs in about 42.8% of cases. It is thus suggested that there is a link between high levels of estrogen and progesterone in pregnancy and the stimulation of CRC proliferation. A second consequence would be the discovery of advanced stage neoplasia, due to the high titres of sex hormones. Cox-2 enzyme. also find in pregnant women the essential role of the Cox-2 enzyme and derivatives in the early stages of pregnancy (ovulation, fertilization, implantation, and decidualisation) but also in the other stages of pregnancy. Because high levels of Cox-2 are encountered in CRC, in was made a hypothesis of an interrelation between the two phenomena. In addition to genetic involvement, other etiological mechanisms of CRC, environmental or individual, behavioral are incriminated [40-44].

**Obesity**

It is a major risk factor especially for hormone-active women in the pre-menopausal period compared to the post-menopausal one. Because the rate of obesity cases has seen a spectacular increase in the last three decades in the industrialized countries [45-47], the causal-effect link is defined in increasing the incidence of CRC at an increasingly young age. The mechanism by which obesity induces tumor development, respectively the latency period between aggression and tumor onset, remains unclear. The corroboration of type 2 diabetes and obesity and also the significant increase of

diabetes in young adults certify the role of risk factor of diabetic disease in the onset of CRC [48-51]. Eating habits particular to young people in the USA, tripling the fast-food consumption from the 1970s until now, a supercaloric and rich in meat diet, especially in children, makes it plausible that the increased CRC incidence in young adults may be the consequence of this eating behavior [13,52,53]. On the other hand, the consumption of milk has shown a protective effect [54]. Other behavioral factors such as alcohol use and smoking are associated with increased risk of CRC [55-57].

Inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn disease (CD), are well known to be premalignancies in patients with long-term disease, of at least 8-10 years (about 2% of CRC) [58-63]. The presence of IBD in the pregnant woman is similar to the incidence in the general population, the enteral inflammatory pathology appearing in childhood, with a peak of manifestations between 15-30 years. The occurrence of CRC in pregnancy is reported precisely on this background of long evolution of the disease (about 15-20 years), between the peak of the symptomatology and the pregnancy [64] (risk of occurrence of 2-3 times higher than in the population general) [65].

**Pathological Anatomy and Carcinogenesis**

The most common colorectal cancers in pregnancy are epithelial, 90% adenocarcinomas and 10% mucinous adenocarcinomas; the rest are considered rare types [66-68] (Table 1). Interesting to note, however, is the specificity of the young adult for rare types such as various carcinoids or colo-rectal lymphomas. Especially in young women, including pregnant women, colonic carcinoid, squamous rectal cancers and “transitional cell like” rectal cancers are reported [69]. Histo-carcinogenesis of CRC is not yet fully elucidated. Colonic polyps are involved in the onset of CRC. At least apparently, all cases of CRC derive from adenomatous polyps, an aspect confirmed by all epidemiological and clinico-pathological studies [70-73], the adenoma-cancer sequence being proven by current molecular studies. The evolution towards neoplasia crosses the known adenoma / polyp - low / high dysplasia - invasive carcinoma-like lesion cascade [74] (Table 2).

**Table 1:** The main histopathological types of colorectal cancer (Hamilton & all 68 WHO Classification of Tumours of the Digestive System).

Histopathologic Types of Colorectal Carcinoma – World Health Organisation Classification
Adenocarcinoma, NOS (not otherwise specified)
Mucinous adenocarcinoma (colloid) (> 50% mucinous)
Signet ring carcinoma (> 50% signet ring cell)
Squamous cell carcinoma (epidermoid)
Adenosquamous carcinoma
Small cell carcinoma (oat-cell)
Medullary carcinoma
Undifferentiated carcinoma
Other types ( Micropapillary carcinoma, Serrated adenocarcinoma, Cribriform comedo-type adenocarcinoma)

**Table 2:** Vienna classification of gastrointestinal epithelial neoplasia and the sequence of evolution towards neoplasia (Schlemper RJ &all) [74].

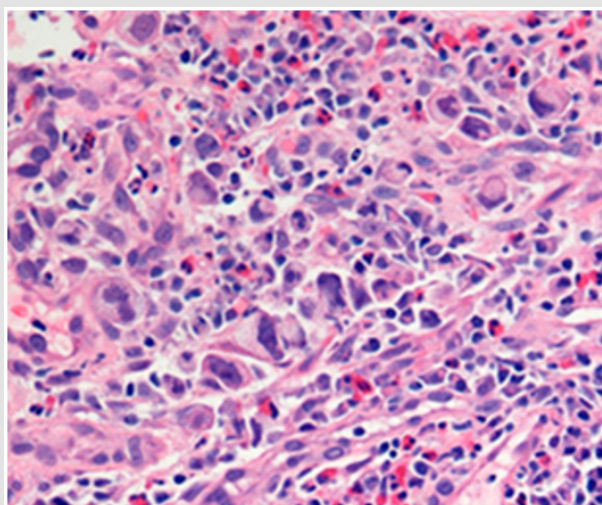
Category	Diagnosis
Group 1	Negative for neoplasia/dysplasia
Group 2	Indefinite for neoplasia/dysplasia
Group 3	Mucosal low grade neoplasia – Non invasive Low grade adenoma/dysplasia
Group 4 Subgroup 4.1 Subgroup 4.2 Subgroup 4.3	Mucosal high grade neoplasia - Non-invasive - High grade adenoma/dysplasia - Non-invasive carcinoma (carcinoma in situ)* - Suspicion of invasive carcinoma
Group 5 Subgroup 5.1 Subgroup 5.2	Invasive neoplasia - Intramucosal carcinoma† - Submucosal carcinoma or beyond

\*Non-invasive indicates absence of evident invasion.

†Intramucosal indicates invasion into the lamina propria or muscularis mucosae.

In the histological criterion of evaluation of neoplasia and, of course, of prognosis, the tumor differentiation type (grading) has a major importance, being considered an independent element of evaluation [75-84] by the World Health Organization: Low Grade - well differentiated and moderately differentiated, High Grade - poorly differentiated and undifferentiated (about 20 % of cases). The better the tumor differentiation, respectively Low grade, the better prognosis is reported [85]. Surbone et al. [86] report in

pregnant women a higher frequency of poorly differentiated and undifferentiated colorectal tumor or the presence of mucinous tumors (Figure 2). Additional specific histological assessment data of the tumor in the pregnant woman such as lymphatic invasion, vascular or perineural invasion, aneuploidy, etc. are missing in various studies, making a consistent assessment impossible, most probably due to the lack of a convenient statistical pool.



**Figure 2:** Histopathologic slide (magnification x40 hematoxylin and eosin) suggestive appearance for poorly differentiated, signet ring cell carcinoma CRC (collection of the clinic).

### Clinical Diagnosis

Clinical manifestations of CRC in pregnancy are masked by characteristic signs of pregnancy, all the more present as the pregnancy approaches the term: diffuse abdominal pain, meteorism, constipation, physical asthenia, possible rectal bleeding. The consequence will be the ignorance of the symptoms and the avoidance of the consultation with a doctor, with the progression of the neoplastic disease so that, most often, the diagnosis will reveal

CRC in an advanced phase. Often, even the doctor can neglect these manifestations, putting them on account of pregnancy-specific complications [87]. As a result, the physician should be alert to any new signs/symptoms, especially its persistence in pregnancy, and to consider the possibility of another pathology, such as CRC. Other less common manifestations would be unnatural weight loss, nausea and/or vomiting, malaise. In the onset of symptoms, it is important to locate the tumor, its dimensions, degree of invasion (metastasis).



Cancer of the right colon are generally bulky, ulcerated, with an important sclerolipomatous peritumoral process, which is why they often appear to be more advanced than they actually are, hemorrhagic, usually with small but chronic bleeding, leading to unexplained anemia. Due to the minimal bleeding, the appearance is occult bleeding, and can only be detected by specific tests [16,88]. The anemia that accompanies the bleeding has the appearance of a iron deficiency anemia, with partial response to iron treatment, and may manifest the signes of weakness, fatigue, dyspnea or palpitations. In comparison, cancer of the left colon are causing most often stenosis, are small in size, causing transit disorders in the form of a constipation that does not respond to treatment, with subocclusive syndrome or even intestinal obstruction. Exceptionally, König-type manifestations may occur in pseudocclusive tumors - a period of severe constipation, with severe meteorism and colicative abdominal pain before the obstacle followed, paradoxically, by numerous diarrhea stools with obvious improvement in symptoms.

Evolution is cyclical, a similar episode can occur at any time. Bleeding often appears dark or maroon-colored and may be mixed with stool. Distal (rectal) neoplasms are rarely occlusive, the main manifestation usually is bleeding with a characteristic aspect: partially degraded blood of hematochezia, mixed with stool or red blood or blood clots before or at the end of defecation, possibly associated with rectal tenesms. This should not be confused with bleeding from hemorrhoids, often present and with a noisy symptomatology in pregnancy. In advanced CRC, metastatic, weight loss, anorexia, physical asthenia, poor health, constitute a symptomatic tetralogy specific to neoplastic cachexia [89]. Objective clinical examination is mandatory. During the inspection, the neoplastic impregnation can be found and, in the conditions of a complicated tumor, most commonly by perforation, a typical presentation is observed for an acute abdomen: patient is holding her hands on the abdomen, posturally bent forward, the respiratory movements are superficial, tachypnea, the abdominal wall is not moving in inhale/exhale.

At the palpatory examination, in the case of the right colon tumors, a tumor localized in the right fossa and right flank may be detected. This is facilitated on the one hand by the superficial situation of the right colon compared to the left one as well as by the important dimensions of the tumors in the right colon, due to the inflammatory phenomena and the appearance of peritumoral lipomatous sclerosis but, on the other hand, as the pregnancy progresses. The maneuver can be made more difficult. In the left colon the tumor is most often hardly detectable, on the one hand due to the deep location of the left colon and on the other hand, because the tumor dimensions that would make palpatory detection possible are only rarely reached before the appearance of complications. The identification of a distended colon, confirmed by percussion, accompanied by abdominal pain, spontaneous or after palpation, may suggest a partial or total obstruction. However,

the clinical interpretation is not easy in pregnant women, especially at an advanced age of pregnancy.

It is also difficult to identify signs of advanced neoplasm (hepatomegaly, ascites, carcinomatosis) or the Sister Mary Joseph sign (palpable umbilical metastasis) but their clinical value is low and non-specific to CRC. The search for peripheric adenopathies, although rarely discovered, such as the Virchow-Troisier sign, is mandatory. Vaginal and rectal examination [90] allow the identification of any lesions, including tumors, up to about 8-10 cm from the anus. Palpation provides data on the location of a tumor in this range, the possible extent of the tumor, the characteristics of the tumor (vegetative, ulcerated), local invasion. Associated with vaginal examination, bidigital palpation of the recto-vaginal septum provides information about the anterior extension of the rectal tumor. The examination of the exploratory finger will allow to appreciate the quality and the appearance of a possible rectal bleeding, facilitating the diagnosis.

### Evolution and Complications

The occurrence of CRC complications in pregnant women causes a poor prognostic factor, both immediately (vital) and also on a long term, both for mother and fetus. CRC evolution has a slow progression (from the onset until it becomes clinically detectable it has a history of about 1.5-2 years). Quite often, the appearance of a complication is relevant for the diagnosis, in the conditions of a completely asymptomatic or at least non-specific evolution, as is the case with the pregnant women. Complete or quasi-complete tumor stenosis causes sub-occlusive or occlusive syndromes. If the tumor volume is important, compression phenomena are possible on the neighboring organs: bladder, ureter, iliac vessels. Tumor perforation can be perforation in the tumor or on the juxtatumoral segment, and diastatic perforation (remote perforation, especially in the region of the caecum and ascending colon, if the ileal valve is competent). When there is a degree of reactivity, the tumor perforation can be covered with the greater omentum and neighboring organs, evolving in a confined space. The result will be a blocked hyperseptic peritonitis - perineoplastic abscess. When the tumor perforation is in the large cavity, the consequence is a diffuse faecal peritonitis, extremely severe and with an unfavorable prognosis.

Chronic bleeding is not considered an evolutive complication; only severe bleeding, externalized as lower digestive hemorrhages (hematochesis). Frequently, bleeding is not very abundant, it stops spontaneously and recurs capriciously, unrelated to food or other phenomena. That is why it is considered the mildest of the evolutive complications of colon cancer. In evolution, the tumor invasion in the neighboring organs allows the erosion of histological barriers with the establishment of internal fistulae in the cavitary organs (stomach, duodenum, small bowell, bladder) or externally, to the abdominal wall. Neoplastic metastases are evidence of a late-

stage disease: lymph node and hepatic metastases, peritoneal carcinomatosis and carcinomatous ascites and, more rarely, metastases in the lungs, bones, ovaries. Some complications are caused by the interference of the body with the metabolism of the atypical process, leading to severe hypoproteinemia with cachexia, severe hydro-electrolytic disorders in the occlusive clinical forms. Acute symptoms and symptoms of the neighboring organs can occur acute cholecystitis, acute appendicitis, revealing the real diagnosis.

## Paraclinic Diagnosis

### Screening Tests

In many countries, in last years, fecal occult blood testing (FOBT) through the Haemocult test in pregnant women is common use. The test is more specific for left colon cancers and can cause false positive and false negative results (consumption of red meat, broccoli, iron medication, aspirin or derivatives, anticoagulants, etc.) [91-93]. Even in ideal conditions, only 5-10% of patients tested were found to have CRC and another 20-30% were found to have adenomatous polyps [94-96]. The false negative results keep the patients in observation for the repetition of the method, and the false positive results are confirmed by the extension of the explorations. When possible, the pregnant woman enters a surveillance and reconfirmation program through a new test and is subsequently further investigated [97,98].

### Laboratory Tests

Without offering a diagnosis of certainty, they highlight changes that suggest a neoplastic pathology: unexplained chronic anemia (without another detectable cause), which takes the form of a chronic blood loss [99,100], hypochromic, microcytic, hypsideremic, leukocytosis with a predominance of neutrophils resulting from tumor superinfection and increased inflammatory indices (ESR, fibrinogen). In case of increased alkaline phosphatase, aminotransferases and bromsulphaphtale retention, the possibility of liver metastases is suspected; high levels of alkaline phosphatase concomitant with those of calcium raise the suspicion of bone metastases [101]. Immunological tests (carcinoembryonic antigen -ACE,  $\alpha$ -fetoprotein, CA 19-9) are lacking in specificity, having no diagnostic value in the early stages, but their role is gaining importance in postoperative oncological monitoring, signaling the occurrence of metastases [102-108]. Currently, their value is normal in pregnant women, not being influenced by pregnancy, or there is only a slight increase, without pathological significance [109]. However, high levels of tumoral markers are correlated with a poor prognosis. After complete colic resections, the values should normalize. However, persistent high values suggests that the surgery was not curative, insufficient and, of course, overestimated [110,111]. Return to normal values after surgery, followed after a while by a significant increase, suggests recurrence [112-114].

## Barium Enema

Radiological examination of the lower GI is used very successfully in the diagnosis of CRC, but the pregnant woman represents a particular situation that limits the medical indication of this method only in exceptional cases. Irigography is criticized because of the mutagenic, teratogenic and carcinogenic effect of ionizing radiation. The appearance of the side effects above depends on the dose administered (measured in cGy), the conformational structure of the pregnant woman, the trimester of pregnancy, the treatments administered, etc. Current data recommends avoiding radiation greater than 5-10 cGy. Up to this irradiation threshold, the risks are associated with a low level of mutagenicity (stochastic biologic effects) and has no "non-stochastic" type effects (malformations, developmental pathologies) [115-117]. The average dose of irradiation per case is only 0,3 cGy, well below the recommended threshold for pregnant women.

However, in the first trimester, in fact the most important and risky period for the fetus, parsimony is recommended in the indication for barium enema. The diagnostic sensitivity of the method is about 83%, slightly lower than that of colonoscopy [118]. The method can be supplemented by air insufflation, which allows double-contrast examination (Fischer test). Barium enema provides information about the location of the tumor, their number, the tumor impact on the digestive tract and an overall configuration of internal morphology, extremely useful in therapeutic decisions. A defect of the technique is due to the particular situation in pregnant women, especially in the advanced stages of pregnancy, altering the diagnostic interpretation by masking and possibly displacing the colon and/or tumor. Barium enema also has obvious advantages: cheap, less invasive and safer compared to colonoscopy (extremely low perforation risk - about 1 per 25000 examinations) [119].

Endoscopy (rectosigmoidoscopy, colonoscopy) allows direct, macroscopic diagnosis and by direct biopsy sampling of the lesion. The risks of the method are not to be neglected [120,121]: placental abruption as a consequence of luminal insufflation with pressure on the uterus, various fetal injuries secondary to hypotension or maternal hypoxia during exploration by deep sedation, teratogenic effects due to the administered medication, enteral perforation due to difficulty technique, etc. In a study on 192 cases, to minimize maternal-fetal risks, Dark and Campbell [122], recommend: administration of oxygen to the patient during the maneuver, gentle handling and minimization of insufflation pressure, positioning the pregnant woman in the left lateral decubitus to lower the pressure in the inferior vena cava, sedation with meperidine and not with diazepam/midazolam due to the minimal effect on the fetus, fetal cardiac monitoring [123]. Colonoscopy is indicated only in case of CRC suspicion.

Recto-sigmoidoscopy or partial colonoscopy is convenient due to the patient's much greater tolerance for exploration, minimal risk

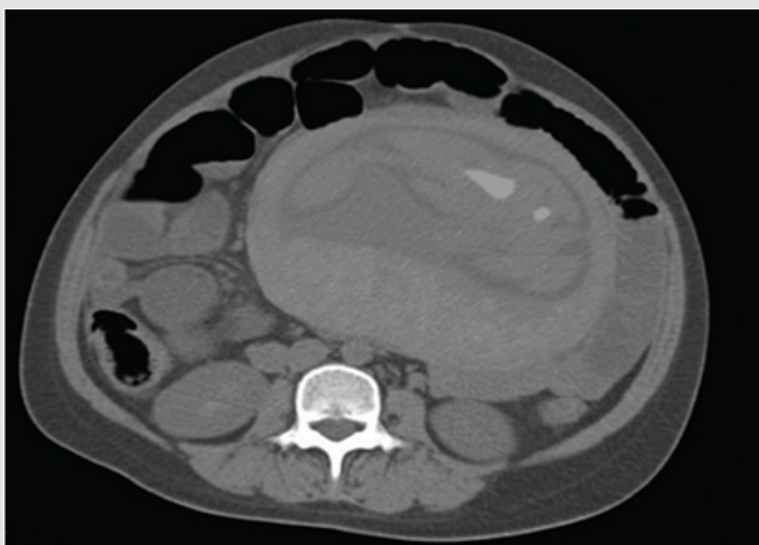
for possible congenital malformations or abortion induction [124-126], fast and effective, but provides information for lesions up to about 40 cm from the anocutaneous margin [125,127]. However, the risk of leaving synchronous lesions above the distal tumor (5% of cases), makes recto sigmoidoscopy a “second hand” method, which can be used whenever we cannot perform a colonoscopy. Therefore, the colonoscopic examination should not stop at the first lesion encountered and should progress as much as possible. In general, it is recommended that biopsy prelevation should be made from the edges of the ulcerative lesion. The association of the endoscopic ultrasound examination (intraluminal ultrasound) confers valuable information in assessing the degree of parietal invasion by the tumor, allowing the evaluation of the T index in the TNM classification. Completing the colonoscopic examination with the cytological examination obtained by direct brushing of the tumor through the endoscope or the cells exfoliated from the enema fluid or during the endoscopic examination allows the diagnostic index to be increased [128-129].

Standard abdominal ultrasound has a limited diagnostic role, usually for the assessment of staging (M index - metastases): liver metastases (sensitivity of 75-80%) or other abdominal disseminations. It can be used to guide needle biopsies. The US cannot detect metastatic determinations of sizes below one centimeter. Endoscopic ultrasound, especially the transrectal ultrasound, brings additional details for T (parietal invasion) and N (lymphadenopathy) indices from TMN staging. The comparison regarding the accuracy in the evaluation of T, on large studies, shows that for CT the value is 75% and 85% for echo-endoscopy, respectively [130-138]; for N the values are between 54% for CT respectively 73% - 83% for EUS. In assessing regional lymph node status (N1), recent papers [131-134,139] shows a positive predictive value of 86%. A special indication of EUS: anterior or large rectal tumors, which can invade the rectum-vaginal septum and vagina, contraindicating natural birth [140].

Whenever the ganglionic aspect of the EUS is abnormal, the guided needle becomes mandatory (EUS FNA) - “gold standard”. The combination of the two methods increases the positive prediction factor to 95% but there are few studies and experience in this regard. In the anterior secondary invasion that is not more than 3 cm away from the rectal parietal border, EUS is considered much more valuable compared to CT. In contrast, as the distance increases, EUS can no longer provide data on possible secondary determinations, due to low tissue penetrability or, the presence of obstructive tumors (up to 50% of cases) that cannot be exceeded by the exploratory endoscope, or by the oncological treatments that also interfere with the method [133,141-144].

### Computed Tomography

Essential in terms of assessing the staging of TNM in CRC, CT remains the subject of numerous debates. Of course, whenever the method can be avoided, it is good not to use this technique. If CT can be evocative for a diagnosis, especially in case of a major complication (Figure 3), or as a therapeutic guide, the practitioner should not hesitate to use it, the life of the mother being considered more valuable than that of the fetus (!). What can CT bring to the assessment of neoplasia during pregnancy? First of all, the method allows a three-dimensional evaluation of the colon-rectum relations with the adjacent structures. Secondly, the appreciation and demonstration of complications that are not apparent or lead to a rapid adverse evolution of the mother in the absence of a clear or obvious diagnosis, which puts her life in immediate danger, especially in the absence of rapid and effective treatment (perforations, obstructions, etc.) [145,146]. Third, an appreciation of staging. After an initial enthusiasm, in which CT was accredited with an accuracy of 85-90% in assessing the T index from TNM staging, high-rigorous studies [146-149] proved a much lower rate, between 50-70%, dependent of the lesion stage (the accuracy for the T4 lesion is much better compared to that of T2 or T3).



**Figure 3:** Pregnant CT scan showing an occlusive complication of a recto-sigmoid junction CRC (collection of the clinic).



Overestimation of the T-index is the most common problem [150]. Particularly for rectal cancer and especially in pregnancy, when zonal changes are important and may alter the accuracy of the method, inflammatory perirectal fibrous bundles may be confused with perirectal tumor infiltration, overestimating the tumor [151]. The dimensional limits of the method are somewhere around 1 cm. Therefore, the detection of lymphadenopathy (N index) remains a problem as long as they do not exceed this value. That is why the specificity in detection N is only 45% (!) [145]. The essential role of CT is to assess the M index, identifying liver metastases with an accuracy of 85% and a specificity of 97% [148]. The data are somewhat superimposable with those obtained by MRI [149]. Over the last 40 years CT has been contraindicated in pregnant women due to teratogenic and carcinogenic effects on the fetus. The introduction of spiral CT drastically diminished the irradiation during the exploration, an entire segment (eg abdomen or pelvis) being traversed in about 17-19 seconds for sectional fields at 1.25 mm. For this reason, the CT method has been re-evaluated for use in pregnant women.

The teratogenic effect of CT radiation is non-cumulative (non-stochastic). The most susceptible period to the teratogenic effects of CT irradiation corresponds to the organogenesis period, especially during the 2-15 weeks of pregnancy. Teratogenic complications include [152]: mental retardation, growth deficiencies, microcephaly, microphthalmia, behavioral deviations, cataracts. The threshold irradiation dose [153], under which no teratogenic effects occur, it is not clearly known but it appears to be between 5 and 15 cGy. During a spiral CT the dose administered to the fetus is variable [154-158], depending on a number of elements (eg examination parameters), between 2.9-4.4 cGy, irradiating dose well below the critical threshold at congenital malformations [159]. The carcinogenic effect over time of CT is cumulative (stochastic), there is no threshold dose. There is also a dependence between the time of radiation exposure in pregnancy and the risk of carcinogenesis. The smaller the pregnancy, the higher the risk [160,161].

It is estimated that at the average dose used (2-5 cGy) for a CT, the risk of childhood cancer doubles. However, the value is very low, the recommendations of the American College of Obstetrics and Gynecology are significant: "very low carcinogenic risk, abortion is not recommended" [157,158,162,163]. A problem also arises regarding the use of contrast media. No mutagenic/teratogenic effects were found in the *in vivo* studies [164,165]. The use of iodinated contrast media would have a potential to develop fetal hypothyroidism [166,167] but these reluctances have also been removed by newer studies [168,169], which do not find any side effects in the thyroid function of the child after exposure to them in the fetal period. A promising option for the evaluation of pregnant women is virtual colonoscopy (CT colonography) due to the use of low doses of irradiation and a reduced "aggressiveness" of the method [170,171]. With an excellent accuracy of 81% and a sensitivity of 93%, the technique will have a lot to say in the

future but, for the moment, there are not enough data regarding the application of the method to pregnant women.

Magnetic resonance image is the variant used in pregnant women instead of CT to assess the stage of CRC, having the possibility to provide: information and complex topographic relationships (in three planes), allows the differentiation of tumor recurrences from postoperative fibrous remodeling. It is considered that regarding the staging indices of remote determinations (N and M), the method has similar CT limitations but with much higher costs [148]. The landmarks to be followed are the same as those in CT exploration. The major disadvantage is the presence of artifacts, secondarily induced by enteral peristaltic movements, respiratory movements, with degradation of image quality (scanning takes between 5 and 10 minutes). A newer innovation, endoscopic MRI (!), is at least as effective as EUS in assessing parietal tumor invasion [172-174]. Some studies find a significant improvement in the accuracy of the T-index assessment, with a sensitivity of 100% and a specificity of 86%. The lack of the method is the poor identification of the central or intermediate ganglia (mesenteric, rectal, etc.); here, the classical MRI is much superior [175-177].

MRI also plays an important role [178,179] in accurately predicting circumferential parietal extension (86%) (sensitivity 94-100%, specificity 85-88%) as well as in assessing mesorectal invasion in rectal cancers [180-182], both of which are prognosis and surgical management criteria. There is a controversy regarding the safety of the method in the case of pregnant women, for possible teratogenic effects of magnetic fields and a possible acoustic damage to the fetus. *In vivo* studies on animals of Heinrichs et al. [183] and Tyndall [184] respectively showed the presence of malformations following exposure to magnetic fields (eg ocular malformations), the death or malformations of embryos when the exam is performed during organogenesis [185]. As a result, although no similar effects have been shown in humans, the guidelines of the National Radiological Protection Board from UK [186] recommends: "it is prudent to avoid MRI in pregnant women during the first three months of pregnancy". The possible acoustic effects induced in the fetus by the high sound level during MRI, are more theoretical, without really constituting an obvious threat [187,188] and regarding the contrast medium, no teratogenic effects have been reported [189,190].

In conclusion, in the first trimester of pregnancy MRI will be performed especially for maternal and less fetal indications. The method is preferable to any other method of investigation that uses ionizing radiation [191]. Regarding other CRC diagnostic methods using nuclear techniques, such as PET-CT, these are not in the current use for assessment in pregnant women but, for selected cases, some specific recommendations can be made (18F-FDG dose reduction, the use of the 3D technique that would allow the decrease of the 18F-FDG dose, a good hydration, attenuation of CT voltage, etc). The role of PET-CT in the evaluation of CRC is to identify the



tumor site and assess the degree of distant invasion (metastatic lymphadenopathy, distant metastases). Technological development has allowed the cumulative radiation doses to the fetus during and after PET-CT to be at absolutely convenient levels (between 1 and 2 cGy), comparable or even lower than those administered by spiral CT [192-194].

**Table 3:** Classification list for CRC Stage – 1. American Joint Committee on Cancer (AJCC) and the International Association of Cancer (UICC) - TNM classification, 2. Duke and 3. Modified Astler-Coller system.

Classification List for CRC			
	Dukes	Astler-Coller	TNM
Tumor invasion confined to the mucosa	A	A	Tis, N0
Tumor invasion limited to the submucosa, no lymph node involvement	A	B1	T1, N0
Tumor invasion limited to the submucosa, lymph node involvement	C	C1	T1, N1-2
Limited tumor invasion into the muscle layer, no lymph node involvement	A	B2	T2, N0
Limited tumor invasion into the muscle layer, lymph node involvement	C	C1	T2, N1-2
During the whole muscle layer tumor involvement, no lymph node involvement	B	B2	T3, N0
During the whole muscle layer tumor involvement, lymph node involvement	C	C2	T3, N1-2
Tumors have kept the neighboring organs, no lymph node involvement	B	B2	T4, N0
Tumors have kept the neighboring organs, lymph node involvement	C	C2	T4, N1-2
Other factors notwithstanding distant metastases	D	D	T1-4, N0-2, M1

### Prognosis and Evolution

The prognosis in CRC in pregnant women targets the two partners: mother and fetus. Maternal prognosis for CRC discovered during pregnancy is poor. This is because the tumor is discovered late, in an advanced stage of the disease. Maybe that's why the prognosis of rectal neoplasia is slightly better than that of colon cancer, because distal malignancy is revealed earlier (see clinical signs) [18]. Comparatively, for the same evolutionary stage with the general population, the survival index has no different values [195]. In some studies, cases with 5-year survival are not reported, reinforcing the conclusion of a poor prognosis of CRC in pregnant women [15]. Also, Chan et al. [196] on a review of 42 cases of colic cancers found that the vast majority of pregnant women had died 1 year after the time of diagnostic, the average survival period being less than 5 months (!). Only one patient achieved a survival period of 3.5 years and, of all the patients in the literature studied, none survived up to 5 years. In cases with colic tumors, the presence of a chorionic gonadotrophin secretion associated with aggressive types of neoplasia was noted: mucinous adenocarcinoma, poorly differentiated or undifferentiated cancer cells, extensive invasion in neighboring organs or distance invasion.

Due to these findings, the chain gonadotrophin - aggressive type of cancer - unfortunate prognosis in pregnant women is

### Stage and Prognosis

In current practice, several systems for assessing staging (TNM, Duke or modified Astler-Coller) have been developed; however, the most widespread is the one introduced by AJCC and The Union for International Cancer Control (UICC), the TNM system (Table 3).

suspected [197-201]. The indices of metastatic invasion (liver, ovary, etc.) are similar to those in the general population, the prognosis being negative (about ¼ of women with CRC have secondary ovarian determinations) [202-207]. Fetal prognosis. Hematogenous vertical mother-fetal transmission appears to be possible but is an exceptional event, the placental barrier and the fetal immune system appear to have a protective role. Fetal metastases from colorectal cancers have not been reported [208-210]. More important are the consequences on the fetus after onco-surgical therapies. Induction of malformations, carcinogenic risk, developmental or cerebral disorders, abortion or even fetal death are some of the possible pathologies secondary to chemotherapy or other medical maneuvers; on the other hand, major surgery during pregnancy reports infant mortality rates of about 20% (!) [15,211,212].

### Treatment

The CRC's treatment plan must take into account the interests of two people, the mother and the fetus, so that the "interest" of one does not affect the other, respecting an axiom: treatment as soon as possible for the mother after a birth as soon as possible for the fetus. Therapeutic protocols undergo changes both in terms of the sequence of methods used and times to follow, which is why optimal management requires a multidisciplinary approach

oncologist-obstetrician-surgeon-anesthetist-neonatologist and sometimes surgery in mixed teams obstetrician-surgeon. The family should not be excluded from these decisions, nor should a series of legal, ethical, religious or personal-emotional considerations be neglected. The essential factors on which the therapeutic protocol to follow depends tumor location, stage, tumor complications, type of presentation to the doctor (chronic vs. emergency), age of pregnancy and associated pathologies other than cancer, patient's decision [87]. Colorectal neoplasia is generally a predominantly surgical pathology at the time of disease discovery, especially in conditions of a major complication that leaves no time for a therapeutic alternative (obstruction, perforation, significant bleeding).

The rules of oncological surgery are mandatory: enteral excision depending on the location of the tumor with lymphadenectomy. For right colonic tumors, right ileo-hemicolectomy is performed and for tumors in the left colon, left hemicolectomy, possibly only segmental resection (splenic angle colectomy, sigmoidectomy, recto-sigmoid resection) - Figure 3. For low rectal tumors, the most likely technique is that of Miles abdominoperineal resection of the rectum with a definitive left iliac anus. Diagnosis of neoplasia in the first half of pregnancy, makes ablative surgery necessary, the time too long until the foetus becomes viable substantially increasing the risk of tumor progression. Depending on the tumor stage, abortion to speed up CRC treatment seems to be the option to choose [213]. Until 20-30 years ago, the risk of fetal death or abortion was significant after surgical resections (about 25%), Woods [211] reporting normal newborns in 25 of 32 cases with CRC. Currently, due to the new anesthetic-surgical acquisitions and the laparoscopic approach, the risk of embryo-fetal death has decreased to about 4%; even the risk of abortion has decreased drastically, yet having a rate twice as high as in the general population [214-219].

The risk of malformations is not different from the general population either; however, there is a slightly higher level of low birth weight. Particular situations such as invasion of the uterus or a difficult approach in the pelvis may require the operating team to sacrifice the uterus and, of course, the ovaries [15,215,220]. In complicated or advanced tumors, palliative techniques such as various by-passes or colostomy may be beneficial, allowing the foetus to reach an age which ensures viability. Diagnosis of neoplasia in the second half of pregnancy. The discovery of a CRC between weeks 20-28 most often requires alternative oncological protocols and, only later, once a suitable fetal age is reached, surgery. If the CRC is apparently localized, with operative perspectives, the operative expectation interval is long enough, about 3 months, which is why chemotherapy is the weapon that represents the solution of a surgical delay. Because at the age of 32-34 weeks the foetus is viable in over 95% of cases, as much as possible the birth should be provoked in / after this period. After a period of about 7-10 days necessary to reduce pelvic congestion, surgery is

performed for tumor ablation, respecting the oncological principles already stated above [221].

For CRC ovariectomy is mandatory, the risk of microscopic insemination or remote metastases of Krukenberg type being very high, possibly being recommended to establish with fertility specialists the opportunity of fertility conservation techniques. The existence of particular situations requires the particular protocols. The impossibility of a natural birth, due to a utero-vaginal invasion by a rectal neoplasm with significant invasion to the anterior or a perineotomy with the risk of spreading the neoplasm, require a single operating time, starting by cesarean section and then continued with colorectal resection [87]. A chemotherapy-type oncology protocol option is preferred for cases with advanced, metastatic neoplasms, the purpose being obviously to prolong the mother's life until the moment of a "safe" birth. If the foetus is of a suitable age, chemotherapy provides a therapeutic option, although only palliative, to the pregnant woman and the mother in the postpartum period. In the latter situation, the decision of starting the chemotherapy belongs to the mother, who must understand the risks to the foetus, the limited effectiveness of treatment and, of course, take into account a number of moral, religious, ethical, etc.

The usual CRC regimens use antimetabolites (5-FU, methotrexate, etc.) and alkylating agents (cyclophosphamide, chlorambucil) and the most convenient dual formula, widely used, apparently with minimal effects on the foetus, the combination 5-FU + Leucovorin (folinated calcium) [222]. Vinca-derived antibiotics or alkaloids do not cause secondary fetal defects while etoposide induces pancytopenia and cisplatin hypoacusis or growth retardation. The therapeutic role and side effects of new agents (oxiplatin, irinotecan, capecitabine) are not well explored or documented. For example, Oxiplatin is classified by the Food and Drug Administration in category D toxicity, at risk of fetal injury [223]. Fetal toxicity regarding monotherapy vs. polychemotherapy shows a slight increase, from 17 to 25% in the case of multiple chemotherapy [224]. An option would be the weekly therapy, especially the treatment with doxorubicin, paclitaxel, epirubicin, with minimal hematological effects in the mother and a much faster recovery for childbirth [225,226]. Chemotherapy should not be given after 33 weeks or 3 weeks before birth [227].

A particular case is represented by the low rectal cancers, located up to 10 cm from the ano-cutaneous line. For these, neoadjuvant oncological radiochemotherapy may be a possible solution in pregnant women in the second half of pregnancy. Radiation therapy can induce important side effects: carcinogenesis, mental or physical retardation, even fetal death. New IMRT techniques, with appropriate utero-fetal protection so that the dose of irradiation per pregnancy does not exceed 10 cGy, can provide a therapeutic variant in selected cases [228-231]. However, irradiation is recommended in the postpartum period and only if it is absolutely

necessary during pregnancy, provided that the irradiation area is as far apart as possible from the foetus. Molecular treatments, such as targeted anti-EGFR therapy eg Cetuximab (Erbix), have not been used and there are no studies to date to provide information on fetal side effects.

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