

# ***IBD,***

## ***Infertility &***

## ***Pregnancy***

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# Inflammatory bowel diseases (IBD)

- IBD represent set of chronic bowel disorders on inflammatory basis.
- It includes **Chron's Disease (CD)**, **Ulcerative Colitis (UC)** & **Indeterminate Colitis**.
- CD differs from UC in Localization i.e. CD affects entire GIT, from mouth to anus, while UC is mainly localized in colon & rectum.
- CD lesions also have Segmental Trend, i.e. tracts of healthy mucosa alternating e' tracts of pathological mucosa, while UC has Linear Trend, i.e. all mucosa affected by disease is pathological.

# Pathogenesis of IBD

- Pathogenesis of IBD is multifactorial & includes 3 main causes:
  - Genetic susceptibility
  - Environmental factors
  - Immuno-pathogenic factors
- All causes lead to condition known as Dysbiosis, i.e. Change in intestinal flora which changes GI barrier permeability e' consequent change of immuno-regulatory mechanisms.
- Dysbiosis determines growth of microorganisms that produce metabolic components e' toxic action, able to activate local immune system & therefore to trigger inflammatory reaction in mucous membranes.

# IBD & Infertility

- In addition to **Typical GI Manifestations**, IBDs also present **Extra-Intestinal Symptoms** that can involve numerous organs and systems.
- An example is presence of IBD with **Male & Female Infertility.**

# Infertility



- Infertility is defined as inability to conceive after 12 m. of regular, unprotected sex.
- Notably, most pregnancies occur in 1<sup>st</sup> 6 cycles e' sexual intercourse in fertile phase.
- If this is not the case, subfertility in 1 in 2 couples should be assumed.
- After 12 m. there is talk of infertility & after 48 m. **5%** of couples are definitively infertile with almost zero probability of spontaneously becoming pregnant in future.

# Infertility

- Fertility rates are influenced by multiple factors:
  - Age
  - Acute or chronic conditions
  - Environmental toxins
  - Occupational exposures
  - General lifestyle problems
  - Infectious diseases
  - Genetic conditions
  - Specific reproductive disorders that affect both males & Females

# Infertility

- Infertility linked to female causes could be due to:
  - Peritoneal factors
  - Obstruction of tubes
  - Abnormalities of uterus and / or cervix
  - Ovulatory dysfunctions
- Infertility linked to male causes could be due to alterations in spermatozoa:
  - Pathologies e.g. cryptorchidism or varicocele
  - Structural & functional alterations of spermatozoa e.g. reduced mobility or sperm count
- Sometimes, infertility has no apparent cause.

# Female Infertility



- Infertility rate in large population-based studies of patients e' IBD is similar to that in general population & ranges from **5-14%**.
- However, women e' IBD can have fertility problems essentially for 2 reasons:
  - Psychological problems.
  - Mechanical problems related to repeated surgery.



# Psychological problems



- This mainly concern perception of risk, which influences reproductive behavior.
- In particular, women show concern about:
  - Potential teratogenicity of drugs
  - Risk of abortions and / or malformations
  - Inheritance of IBD
  - Possibility of ectopic pregnancies

# Psychological problems

- One study investigated general attitudes of women e' IBD about fertility, drug use, childbirth and pregnancy.
- The results showed that:
  - 36% believed that all drugs used for IBD are harmful to fetus
  - 46% worried about possible infertility
  - 75% were worried about genetic transmission of disease
  - Additionally, **nearly all** participants were concerned about effects of IBD on pregnancy and effects of pregnancy on IBD symptoms.
- These problems require both medical and psychological support to deal e' situation.

# Are IBD drugs Teratogenic?

- In fact, most of drugs used for treatment of IBD (*i.e. corticosteroids, mesalazine, azathioprine, anti-TNF agents and cyclosporine*) do **Not** show evident signs of teratogenicity.

# Hereditary transmission of IBD

- Current data suggest genetic component is partial, and chances that child will Not develop IBD are very high:
  - 91% if only one parent is affected
  - 60% if both parents are affected
- It is therefore important to emphasize to patients that family history is neither necessary nor sufficient for onset of IBD in children & absolute risk remains very low (1.6% for UC and 5.2% for CD).

# Mechanical Problems

- Regarding problems related to surgical interventions mostly concern formation of adhesions caused by disease itself and/or by repeated surgical interventions.
  - For example, in case of UC treated e' IPAA, **possibility of pregnancy is significantly reduced** due to pelvic adhesions, tubal obstruction or alteration of tubal-ovarian relationship.
  - Some studies showed that **complete unilateral or bilateral obstruction of fallopian tubes was observed in 50%** of women undergoing surgery e' creation of ostomies or anastomosis
  - An **increase in infertility rate from 12% to 26%** was also shown in cases undergoing procto-colectomy.

# Pregnancy



- Pregnancy appears to have beneficial effect on IBD symptoms, especially when it occurs during disease remission.
- Large prospective European study showed that 74% of patients e' CD and 67% of patients e' UC (e' active disease at time of conception) achieved remission during pregnancy.
- However, some patients observe increase in IBD-related symptoms in 1<sup>st</sup> trimester of pregnancy, presumably related to discontinuation of maintenance drugs.
- In other patients, presence of active disease at time of conception increases risk of miscarriage, reduced birth weight & pre-term birth.

# Pregnancy

- Presence or absence of disease during pregnancy also appears to be related to disease status at time of conception.
- In cohort study, it was observed that if conception occurred during remission, risk of exacerbation was comparable to that of non-pregnant patients e' IBD.
- In contrast, when conception occurred during period of active disease, 1/3 of the patients had relapse during pregnancy and > 60% of these patients experienced further worsening.

# Pregnancy

- Long-term effect of pregnancy on symptoms & relapses of IBD is also interesting.
- Numerous studies showed:
  - Reduction in recurrence rate of IBD after 4 y. from pregnancy
  - Reduction in annual exacerbation rates (from 0.34 to 0.18 for UC and from 0.76 to 0.12 for CD)
  - Reduction in rate of stenosis and resection.
- Mechanisms potentially involved could be due to:
  - Hormone Relaxin
  - Effect of pregnancy on immune response
  - Fetus-maternal HLA disparity



# Male infertility

- In general population, drugs are responsible for erectile dysfunction in up to 25% of cases.
- In particular, drugs related to this problem are not those for ttt of IBD but those for ttt of anxiety & depression associated e' IBD.
- Only drug showed to cause male infertility is sulfasalazine
  - It causes reversible & non-dose related sperm abnormalities (oligospermia, abnormal morphology & decreased sperm mobility).
  - It also causes infertility rate up to 60%, may be due to impaired sperm maturation & oxidative stress due to sulfa-pyridine constituent of drug.
- Male fertility is restored 2 m. after stopping sulfasalazine or switching to other mesalamine preparations.

# Male infertility

- There are also surgical complications in men that can compromise fertility;
  - For example, procto-colectomy with IPAA appears to be associated with sexual dysfunction (e.g. erectile dysfunction, retrograde ejaculation & anejaculation)
  - Incidence of erectile dysfunction or retrograde ejaculation in those patients is **25.7%**.
  - This is linked to parasympathetic & sympathetic nerve damage during surgery, but sometimes due to anatomical changes, fibrosis or postoperative psychological factors.

# Take Home Message



- Presence of IBD has major impact on both female and male fertility & also affects pregnancy.
- IBDs affect female infertility through mechanical problems related to repeated abdominal surgery and psychological causes.
- Use of IVF in cases with mechanical cause of infertility could partially solve problem.
- Furthermore, psychological problems greatly influence woman's decisions about becoming pregnant.

# Take Home Message

- There are studies showed how pregnancy can lead to reduction in flare-up of pathologies even in long term.
- Studies indicated that remission of symptoms during pregnancy is linked to moment of conception.
- Furthermore, women e' active disease, had increase in rate of spontaneous abortions, pre-term pregnancy and low birth weight.
- Therefore, it would be desirable to continue therapies during pregnancy considering that:
  - Risks related to pregnancy are closely related to presence of active disease
  - Most of drugs used for IBD show low risk of fetal abnormalities

# Take Home Message

- In men e' IBD, main cause of infertility is linked to drug Sulfasalazine, but problems related to Surgery also greatly affect, in particular erectile dysfunctions occur in men undergoing IPAA.
- Further studies are needed to understand what are real mechanisms underlying infertility in subjects suffering from IBD & to plan therapeutic strategies aimed at overcoming this problem.



***THANK YOU***