HUMANITAS
RESEARCH HOSPITAL

UNIVERSITÀ
DEGLI STUDI
DI MILANO

Sintomi gastroenterologici nella donna in età fertile e in gravidanza – Utilizzo dei criteri Roma III

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Outline

1. Gastrointestinal manifestations in pregnancy
2. Irritable bowel syndrome/Inflammatory bowel disease
3. Rome III criteria and GRAAL study
4. Conclusions

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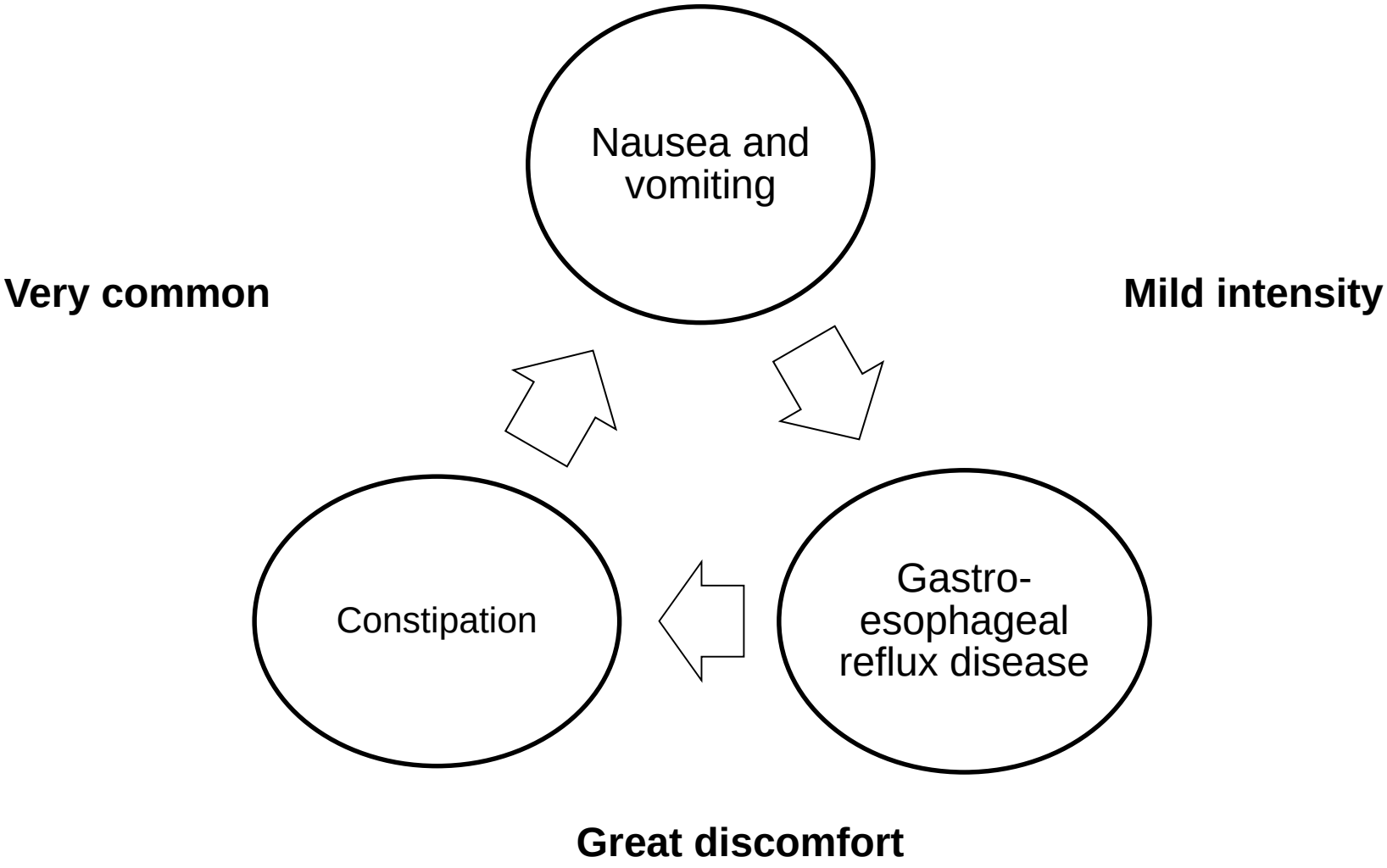
Gastrointestinal symptoms in pregnancy



Nausea and vomiting

- Affects 50–90% of pregnant women
- More often during the first trimester and, in up to 15% of the cases, beyond 15 weeks
- Mild to severe or even unremitting (hyperemesis gravidarum) in 1%
- First cause of hospitalization in the first half of pregnancy

Risk factors:	young age
	obesity
	first pregnancy
	smoking
	vitamin B6 deficiency

- Pathophysiology:
  - changes in gastric motility
  - pregnancy-associated alterations of vestibular system, taste and smell
  - behavioral and psychological factors

Selmi C et al, Metabolic Syndrome and Complications of Pregnancy 2015

Nausea and vomiting are highly hereditable in twins

MZ twin pairs n= 540
DZ twin pairs (same sex) n= 534

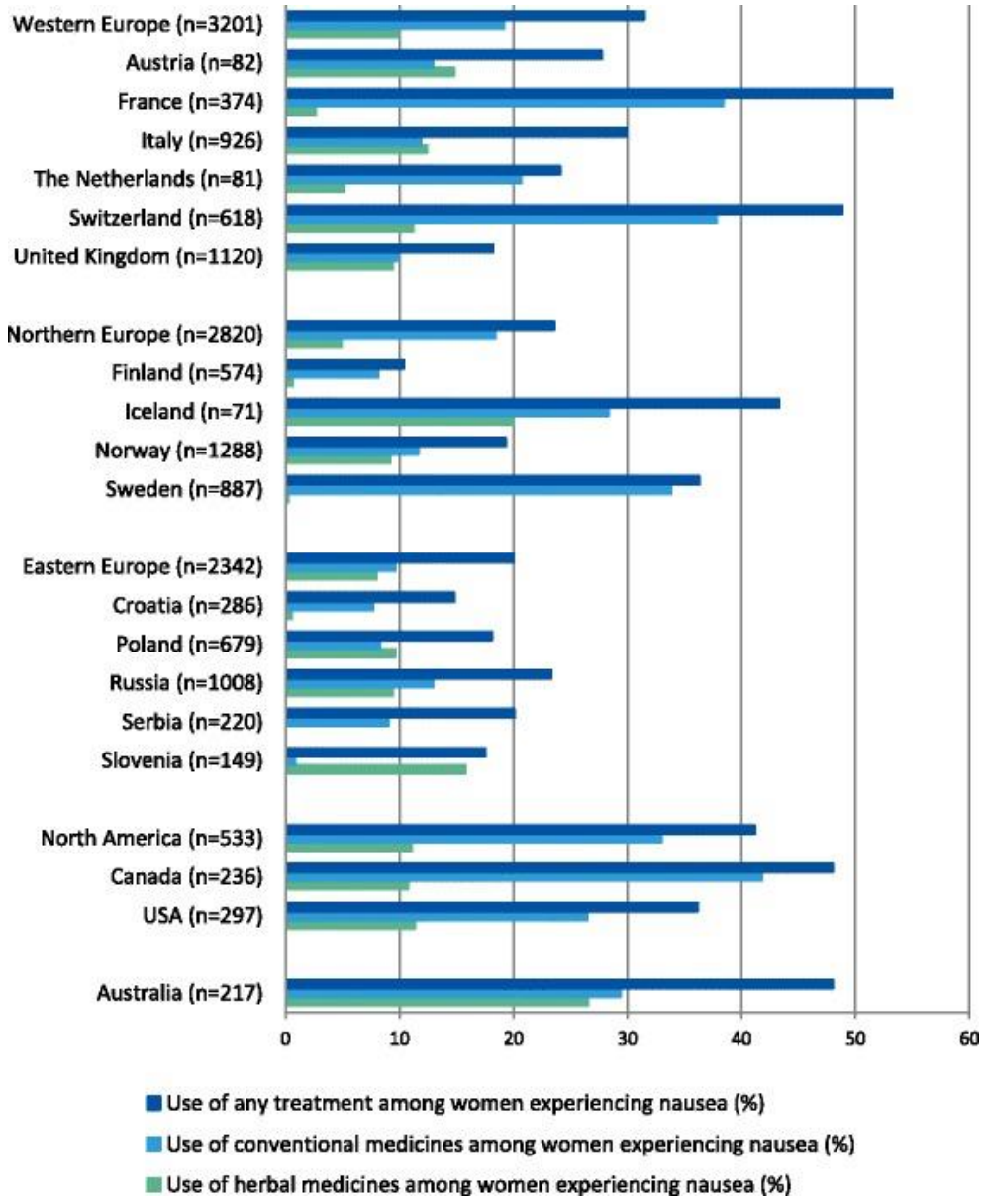
Table 2 Monozygotic (MZ), dizygotic (DZ) twin and twin–sister (TS) thetracoric and polychoric correlations with 95 % confidence intervals (CI) for three NVP phentoypes

	r_{MZ} (95 % CIs)	r_{DZ} (95 % CIs)	r_{TS} (95 % CIs)
Presence	0.75 (0.58, 0.86)	0.29 (0.03, 0.52)	0.43 (0.06, 0.70)
Duration	0.52 (0.37, 0.64)	0.20 (0.01, 0.37)	0.31(−0.04, 0.57)
Severity	0.55 (0.40, 0.67)	0.13 (−0.07, 0.31)	0.33 (−0.01, 0.57)

NVP nausea and vomiting during pregnancy. r_{DZ} and r_{TS} could be equated, yielding in estimates of 0.34 (95 % CI: 0.13, 0.52) for presence, 0.22 (95 % CI: 0.06, 0.37) for duration and 0.17 (95 % CI: 0.02, 0.32) for severity

Colodro-Conde L et al, Behav Genet 2016

Nausea and vomiting



Heitmann K et al, BMC Pregnancy Childbirth 2015

Interventions for nausea and vomiting in early pregnancy

THE COCHRANE COLLABORATION®

- Evidence regarding the effectiveness of P6 acupressure, auricular (ear) acupressure and acustimulation of the P6 point was limited
- Acupuncture (P6 or traditional) showed no significant benefit to women in pregnancy
- The use of ginger products may be helpful to women, but the evidence of effectiveness was limited and not consistent, though three recent studies support ginger over placebo
- There was only limited evidence from trials to support the use of pharmacological agents including vitamin B6, Doxylamine-pyridoxoine and other anti-emetic drugs to relieve mild or moderate nausea and vomiting

Matthews A et al, Cochrane 2015

Nausea and vomiting

Drug	Pregnancy	Lactation	FDA category
Doxylamine succinate/vitamin B_6	No increased risk	Potential toxicity	A
Metoclopramide	No teratogenicity	Potential toxicity	B
Domperidone	Safety unknown	Probably compatible	C
Phenothiazines			
Prochlorperazine	No teratogenicity	Potential toxicity	C
Promethazine	No teratogenicity	Potential toxicity	C
Ondansetron	No teratogenicity	Probably compatible	B

Van der Woude CJ et al, Gut 2014

Food related nausea and vomiting

Infections

Salmonella
Aspergillus
Fusarium
Claviceps
Penicillium
Stachyborys

Food intolerances

Coffee
Fish
Carbohydrates
Proteins

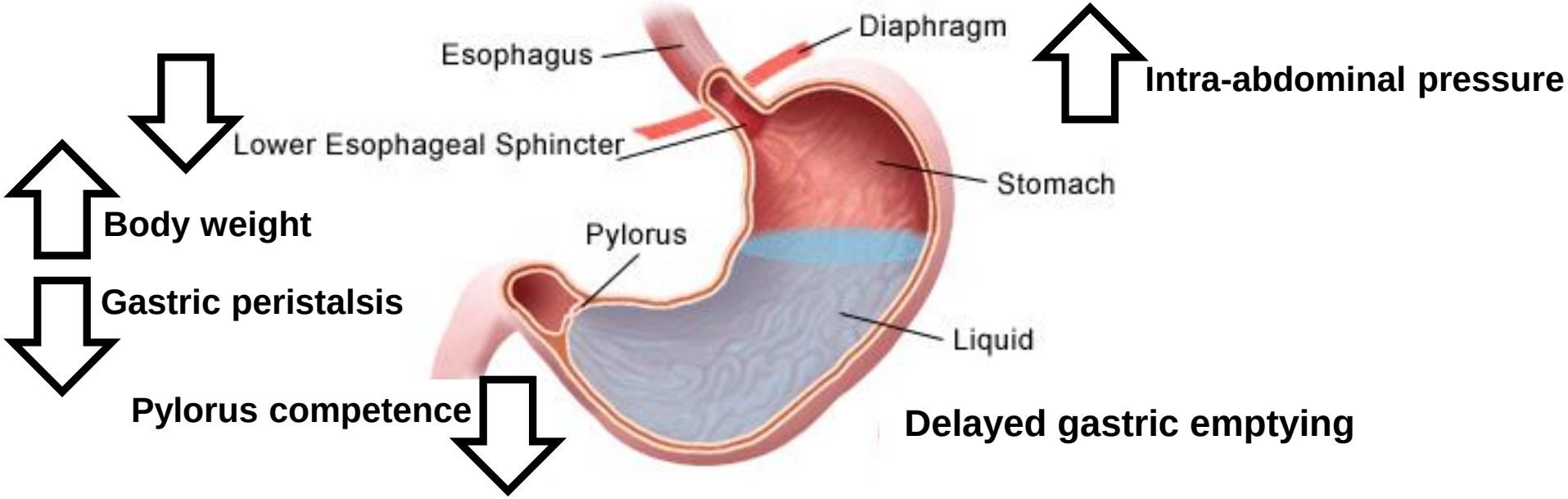
Food components

Monosodium glutamate
Polycyclic aromatic carbohydrates
Heavy metals

Selmi C et al, Metabolic Syndrome and Complications of Pregnancy 2015

Gastro-esophageal reflux disease

- Affects 30%-50% of all pregnancies
- Mostly 3rd trimester
- Women with a history of GERD may experience more severe symptoms during pregnancy



Selmi C et al, Metabolic Syndrome and Complications of Pregnancy 2015

Gastro-esophageal reflux disease

Drug	Pregnancy	Lactation	FDA category
Antacids			
Aluminium containing	Low risk, minimal absorption	All low risk	NA
Calcium containing	Low risk, minimal absorption		
Magnesium containing	Low risk, minimal absorption		
Magnesium trisilicates	Avoid long term or high dose		
Sodium bicarbonate	Not safe, alkalosis		
Sucralfate	Low risk	Unknown	B
H_2 receptor antagonists			
Cimetidine	Low risk	Compatible	B
Ranitidine	Low risk	Probably compatible	B
Others	Limited data, probably safe	Probably compatible	B
Proton pump inhibitors			
Esomeprazole	Limited data, low risk	No human data, potential toxicity	B
Lansoprazole	Limited data, low risk	No human data, potential toxicity	B
Omeprazole	Hazardous in animal studies, probably low risk in humans	Limited human data, potential toxicity	C
Pantoprazole	Limited data, low risk	No human data, potential toxicity	B
Rabeprazole	Limited data, low risk	No human data, potential toxicity	B
Prokinetic agents			
Cisapride	Controlled study; low risk	Limited human data: probably compatible	C
Metoclopramide	Low risk	Limited human data: potential toxicity	B

Van der Woude CJ et al, Gut 2014

Constipation

- Second most common GI complaint in pregnant women (50%)
- 1st-2nd trimesters, diminishing in the 3rd trimester

Risk factors:	low fiber diet
	sedentary lifestyle
	inadequate fluid intake
	bed rest
	medications (iron)
	first pregnancy
	hypothyroidism

Selmi C et al, Metabolic Syndrome and Complications of Pregnancy 2015

Constipation

Lifestyle and diet changes	Exercise Increase water consumption Increase fiber intake Intermittent vs daily iron supplementation
Nonpharmacologic treatment[b]	Probiotics Aloe vera Cascara
Pharmacologic treatment	Psyllium (Metamucil): 2-6 capsules, 2 wafers, or 3-4 g of powder 1-3 times daily Wheat dextrin (Benefiber): 2 teaspoons 3 times daily Polyethylene glycol (MiraLax): 1 capful daily Magnesium hydroxide (Milk of Magnesia): 2400-4800 mg daily (can be divided into 1-3 doses) Sennosides (Senokot): 2-4 tablets orally at night Bisacodyl (Correctol, Dulcolax): 1-3 capsules (can be divided into 1-3 doses)

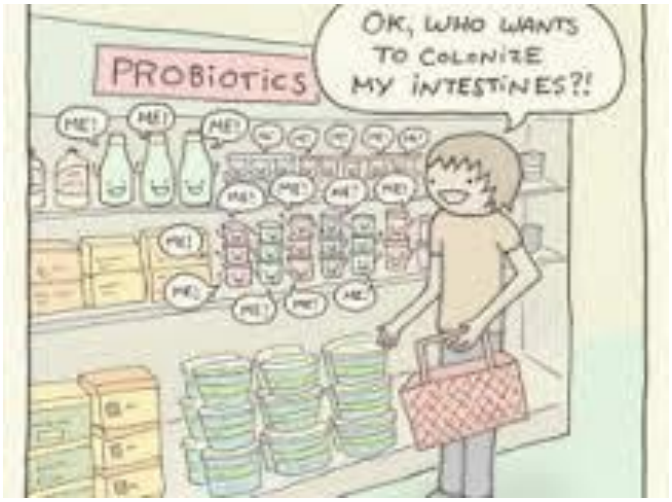
Selmi C et al, Metabolic Syndrome and Complications of Pregnancy 2015

Probiotics

- Live organisms which confer a **health benefit** to the host

- The objective of the use of probiotics is to restore the **balance** in the intestinal **microbiome** by administering commensal **bacteria** (bifidobacteria, lactobacilli, lactococci, streptococci)

- Mechanisms of action:
  - improvement of the intestinal **barrier function**,
  - **modulation** of the immune system,
  - **protection** against pathogens,
  - production of **enzymes and metabolites**



- Probiotics used in combination with prebiotics are referred to as **synbiotics**

- **Prebiotics** are as “non-digestible, but **fermentable**, foods that beneficially affect the host by selectively **stimulating the growth and activity** of one species or a limited number of species of bacteria in the colon

Heppinga H et al, Curr Rheumatol Rep, 2014

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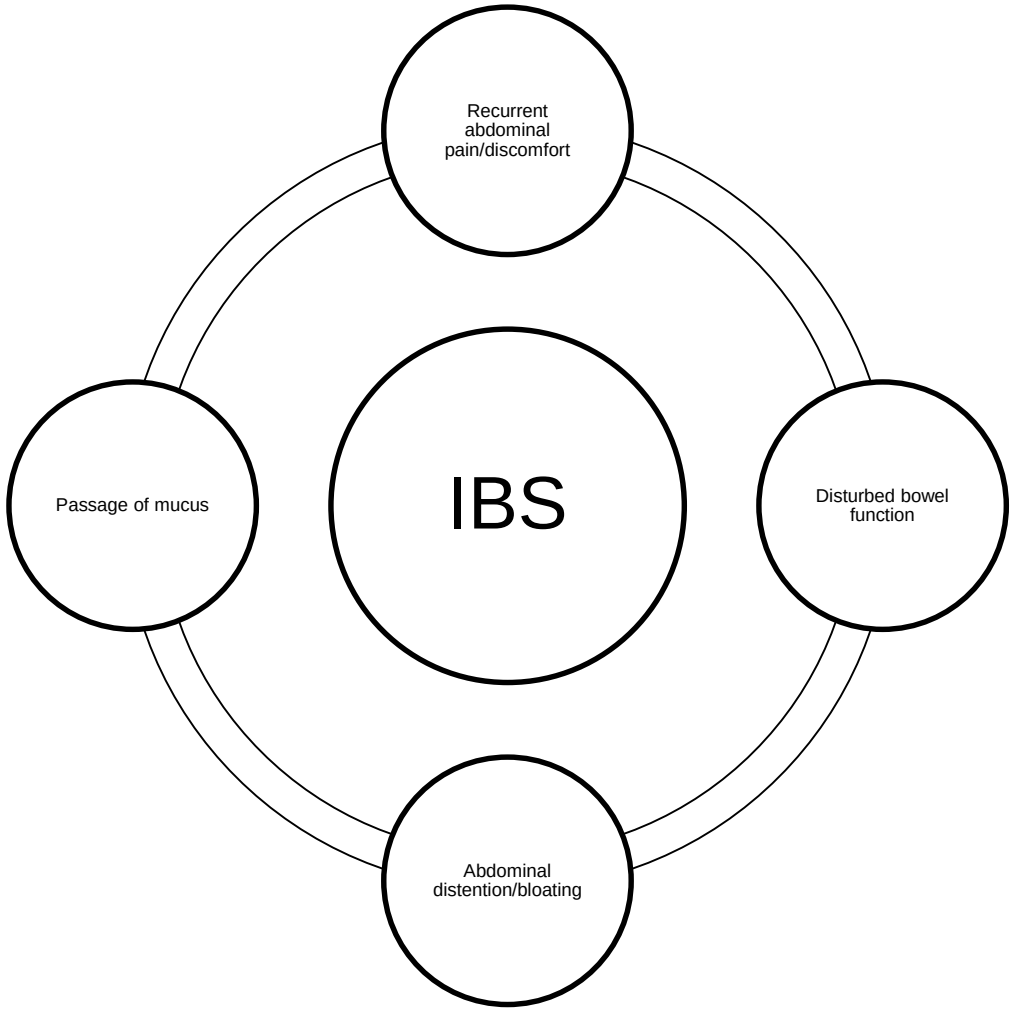
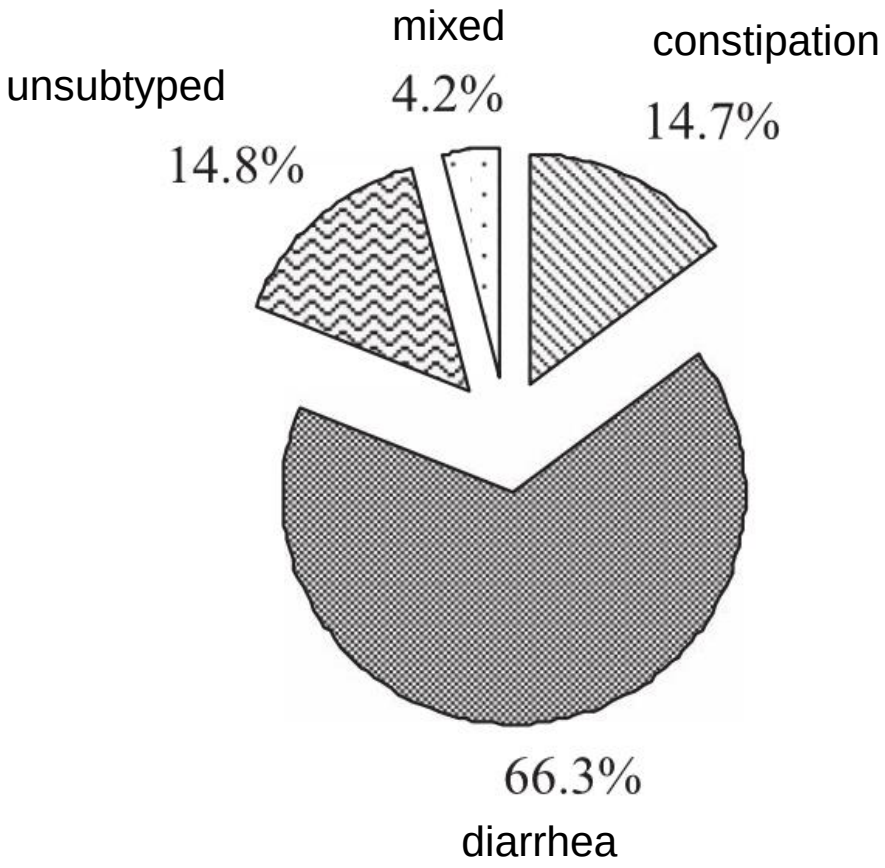
Irritable bowel syndrome



Van der Woude CJ et al, Gut 2014

Irritable bowel syndrome

- Women of childbearing potential represent a significant proportion of IBS patients
- It affects quality of life



Van der Woude CJ et al, Gut 2014
Yao X et al, J Gastroenterol Hepatol 2012

IBS and pregnancy

Table 1 Correlation between hormonal status and irritable bowel syndrome symptoms expression[34]

Status	Hormone levels	IBS and pain related symptoms expression	Ref.
Late luteal phase (premenses)	Rapid decline in estrogen and progesterone levels	Exacerbation of bowel symptoms Increased bloating	[33,34]
Menstruation (menses)	Lowest levels of estrogen and progesterone	Exacerbation of bowel symptoms Increased abdominal pain/discomfort Lower rectal sensitivity threshold	[34,35,37,38,40]
Dysmenorrhea	Disturbances in hormonal interactions at different regulatory levels (lower progesterone level)	Exacerbation of bowel symptoms	[41]
Pregnancy	Physiological hyperestrogenemia and hyperprogesteronemia	Reduced pain sensitivity and alleviation of many chronic pain syndromes Exacerbation of constipation (prolonged gastrointestinal transit)	[27,51,73]
Menopause	Decline in ovarian hormones	Decrease in IBS incidence High prevalence of constipation and somatic discomfort syndromes	[26,53,54]
Oral contraceptives	Estrogen and progestin administration	Reduced abdominal symptoms at menses	[55]
Hormone replacement therapy	Estrogen (and progesterone) supplementation	Increased prevalence of IBS in postmenopausal women during HRT Prolongation of IBS symptoms to a later age	[58]
Oophorectomy	Ovarian hormone deficiency	Exacerbation or occurrence of gastrointestinal symptoms after gynecological surgery	[60]
Men with IBS	Lower level of luteinizing hormone in middle-aged men Elevated level of sex hormone-binding globulin in young men	Generally more prevalent diarrhea (compared to women with IBS)	[66,70]
Transsexual women (male-to-female subjects)	Estrogen/anti-androgen treatment	Development of chronic pain including visceral pain	[72]

IBS: Irritable bowel syndrome; HRT: Hormone replacement therapy.

Mulak A. et al., World J Gastroenterol. 2014

Irritable bowel syndrome

Few studies on IBS and pregnancy

Table 2. Association Between IBS and Spontaneous Miscarriage

Variable	Miscarriage, n	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Model I			
No IBS or depression/anxiety	4500	Reference	Reference
IBS only	1364	1.26 (1.17–1.35)	1.21 (1.13–1.30)
IBS and depression/anxiety	714	1.42 (1.30–1.54)	1.28 (1.18–1.40)

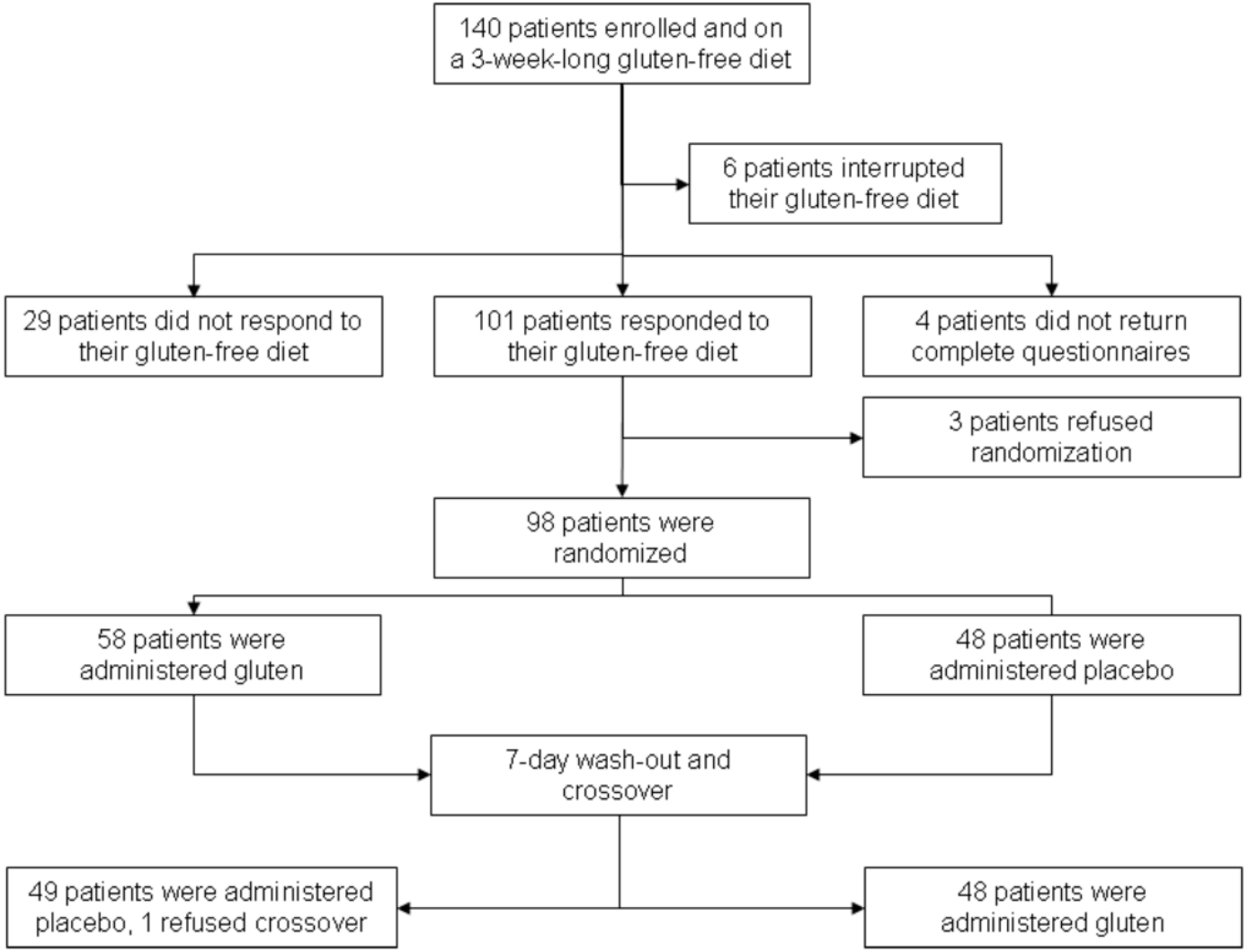
Table 3. Association Between IBS and Ectopic Pregnancy

Variable	Ectopic pregnancy, n	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Model I			
No IBS or depression/anxiety	486	Reference	Reference
IBS only	166	1.39 (1.15–1.67)	1.28 (1.06–1.55)
IBS and depression/anxiety	89	1.61 (1.27–2.04)	1.35 (1.07–1.70)

Khashan AS et al, Clin Gastroenterol Hepatol 2012

Irritable bowel syndrome

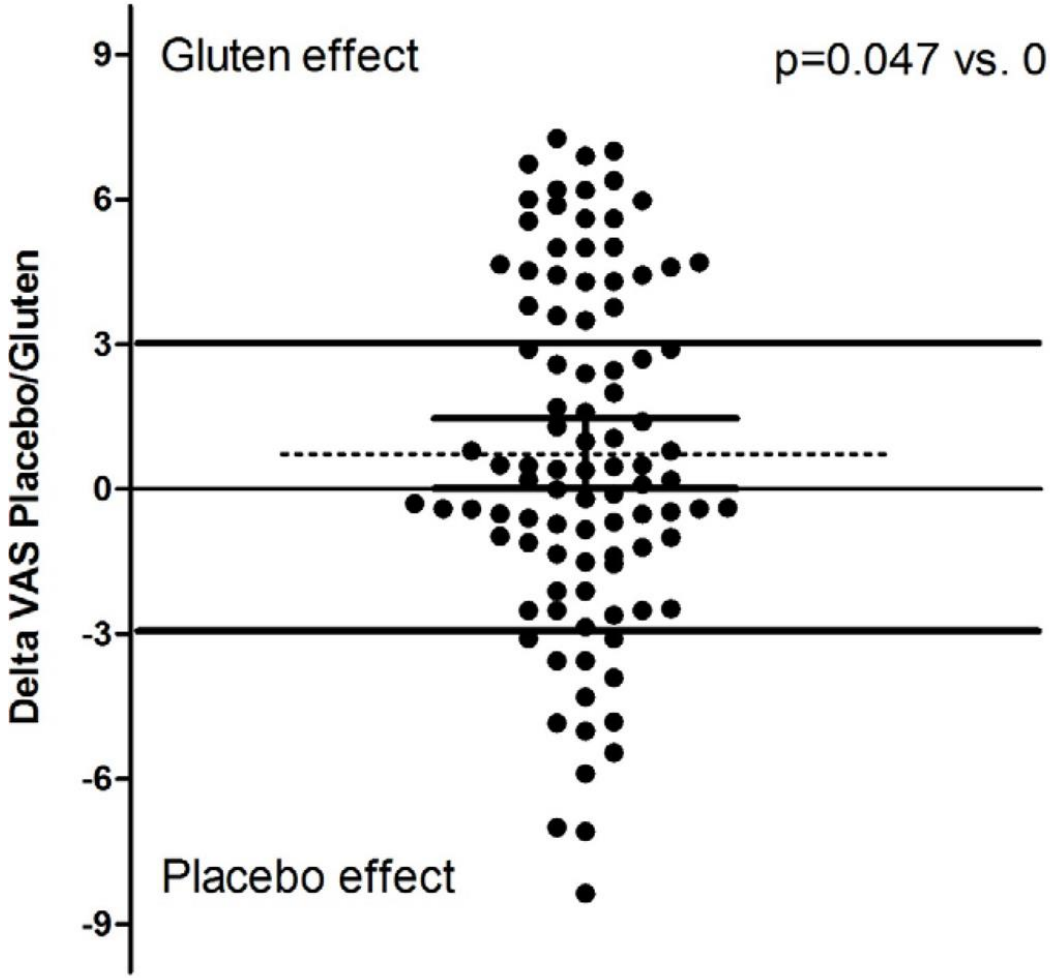
A matter of gluten sensitivity?



Elli L et al, Nutrients 2016

Irritable bowel syndrome

A matter of gluten sensitivity?



Elli L et al, Nutrients 2016

Irritable bowel syndrome

Inflammatory markers

- Some studies have shown that the inflammation and cytokine imbalance may act as potential factors;
- Seventy-four IBS patients diagnosed based on Rome III criteria and 75 gender and age-matched healthy controls were included;
- Cytokines were measured in the serum using enzyme-linked immunosorbent assays (ELISA);
- Patients were classified into groups of IBS with diarrhea: 34, IBS with constipation: 29, and IBS with mixed symptoms: 11.
- Serum levels of IL-6, IL-8 and TNFα were significantly higher in patients with IBS compared to controls ($P<0.001$), not based on IBS subtypes
- Higher serum level of IL-6, IL-8 and TNFα in IBS suggests an important role of cytokines as immune mediators in the pathogenesis of this functional GI disorder (or a misclassification?)

Elli L et al, Nutrients 2016

Irritable bowel syndrome

Few studies on IBS and pregnancy

FBD identified in documentation	Constipation (n = 48)	Diarrhea (n = 5)	Bloating (n = 51)	IBS (n = 46)
Yes (n = 18)	12	3	12	16
No (n = 57)	36	2	39	30

Johnson P et al, Acta Obstet Gynecol Scand 2014

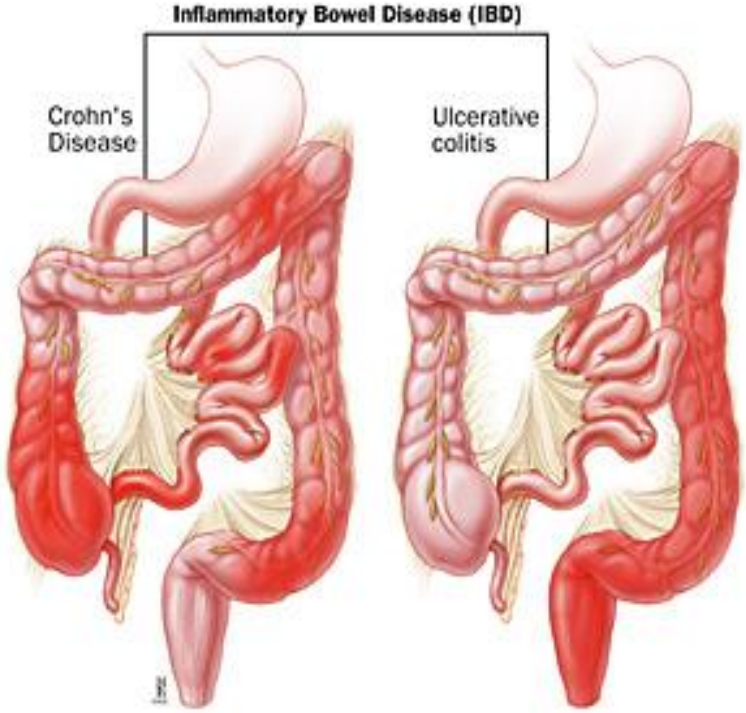
Irritable bowel syndrome

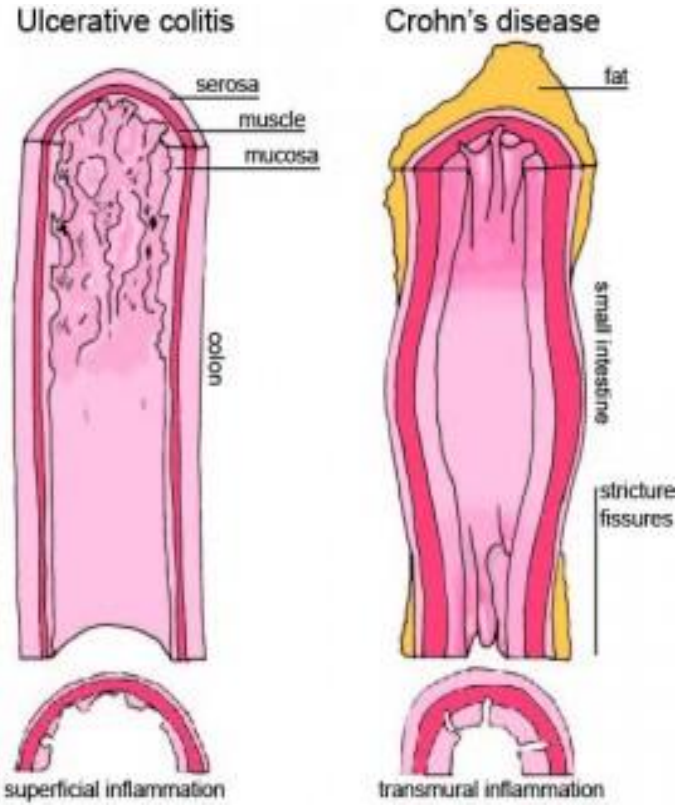
Drug	Pregnancy	Lactation	FDA category
Loperamide	Low risk, avoid in first trimester	Limited data	B
Polyethylene glycol	Low risk	Low risk	C
Sodium phosphate	Low risk, maternal side-effects	Unknown	None
TCAs			
Amitriptyline	Possibly teratogenic	Limited data	C
Doxepin, desipramine	Limited data, avoid if possible		
Alosetron	Avoid if possible, no human data	No data	B
Rifaximin	Avoid if possible, no human data	No data	C
	Teratogenic in animals		
Lubiprostone	Avoid if possible, no human data	No data	C
SSRIs	Fluoxetine: increased risk malformations	Potential toxicity	C
	Avoid in first trimester		
	Paroxetine:risk cardiac malformations	Potential toxicity	D
	Avoid in first trimester		
	Sertraline, citalopram: no increased risk of malformations	Potential toxicity	C
	Cautious during first trimester		

General recommendations: optimise lifestyle. For IBS-C: increased fibre and water intake. For IBS-D: reduced fat and dairy consumption.

Van der Woude CJ et al, Gut 2014

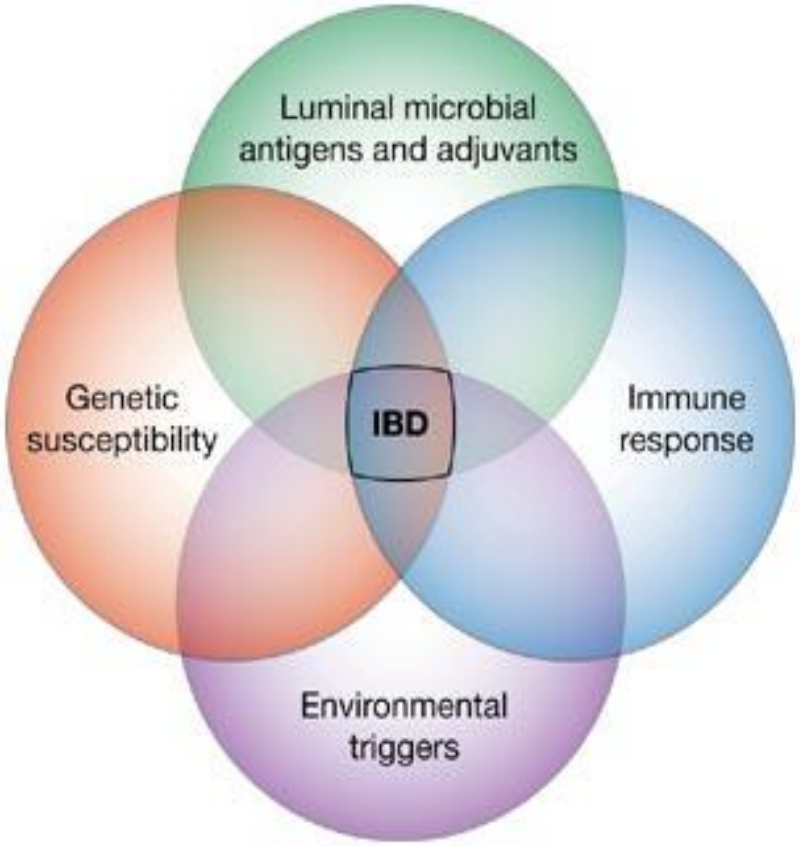
Inflammatory bowel disease





Van der Woude CJ et al, Gut 2014

Inflammatory bowel disease



Etiologic theories of inflammatory bowel diseasese

Persistent specific infection
Dysbiosis (abnormal ratio of beneficial and detrimental commensal microbial agents)
Defective mucosal barrier function
Defective microbial clearance
Aberrant immunoregulation

- Regulation of adaptive immunity (IL-23R, IL-10, STAT, JAK2)

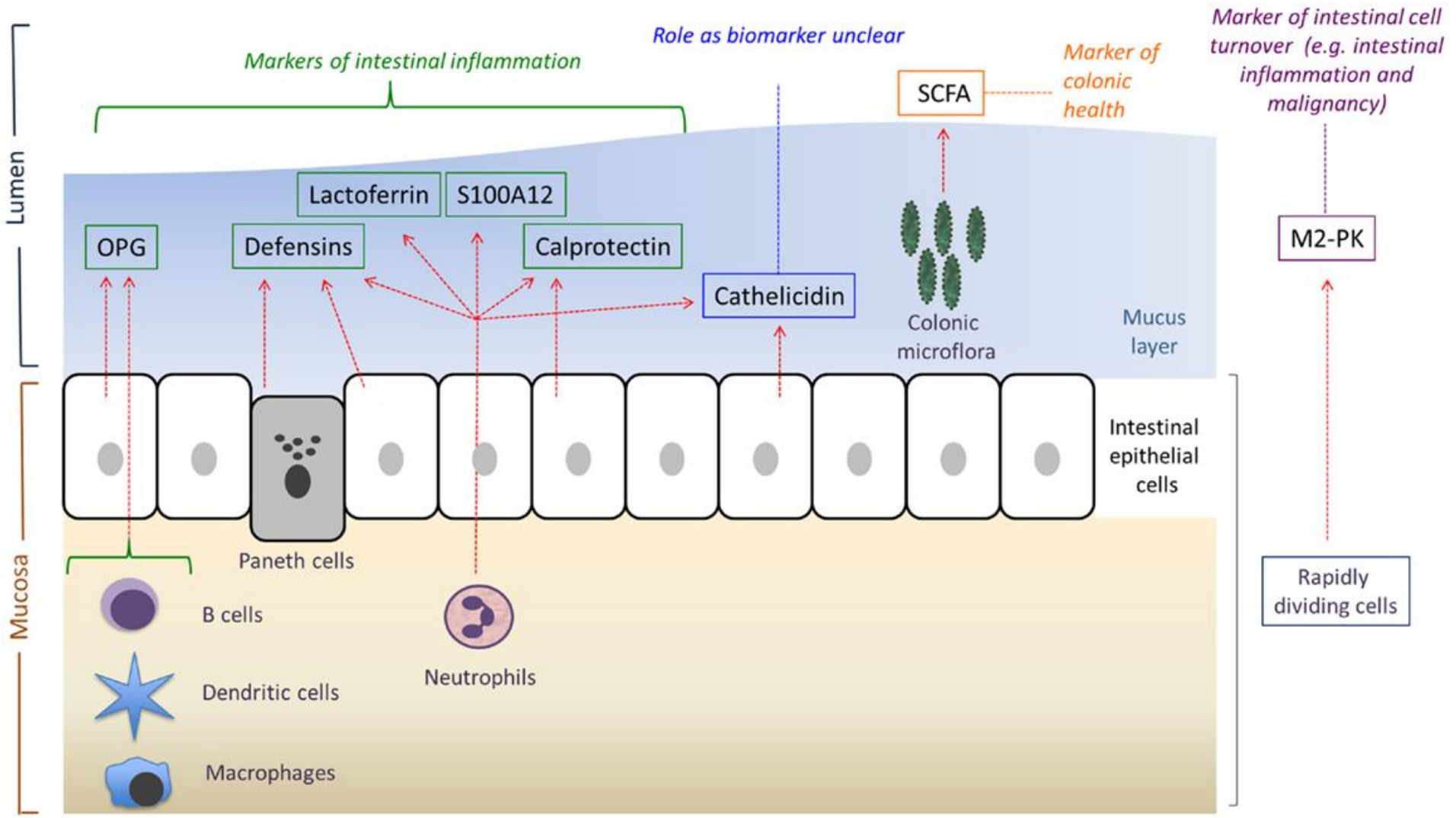
- Regulation of inflammation (CCR6, MST1)

- Regulation of endoplasmic reticulum (ER) stress and autophagy

Van der Woude CJ et al, Gut 2014

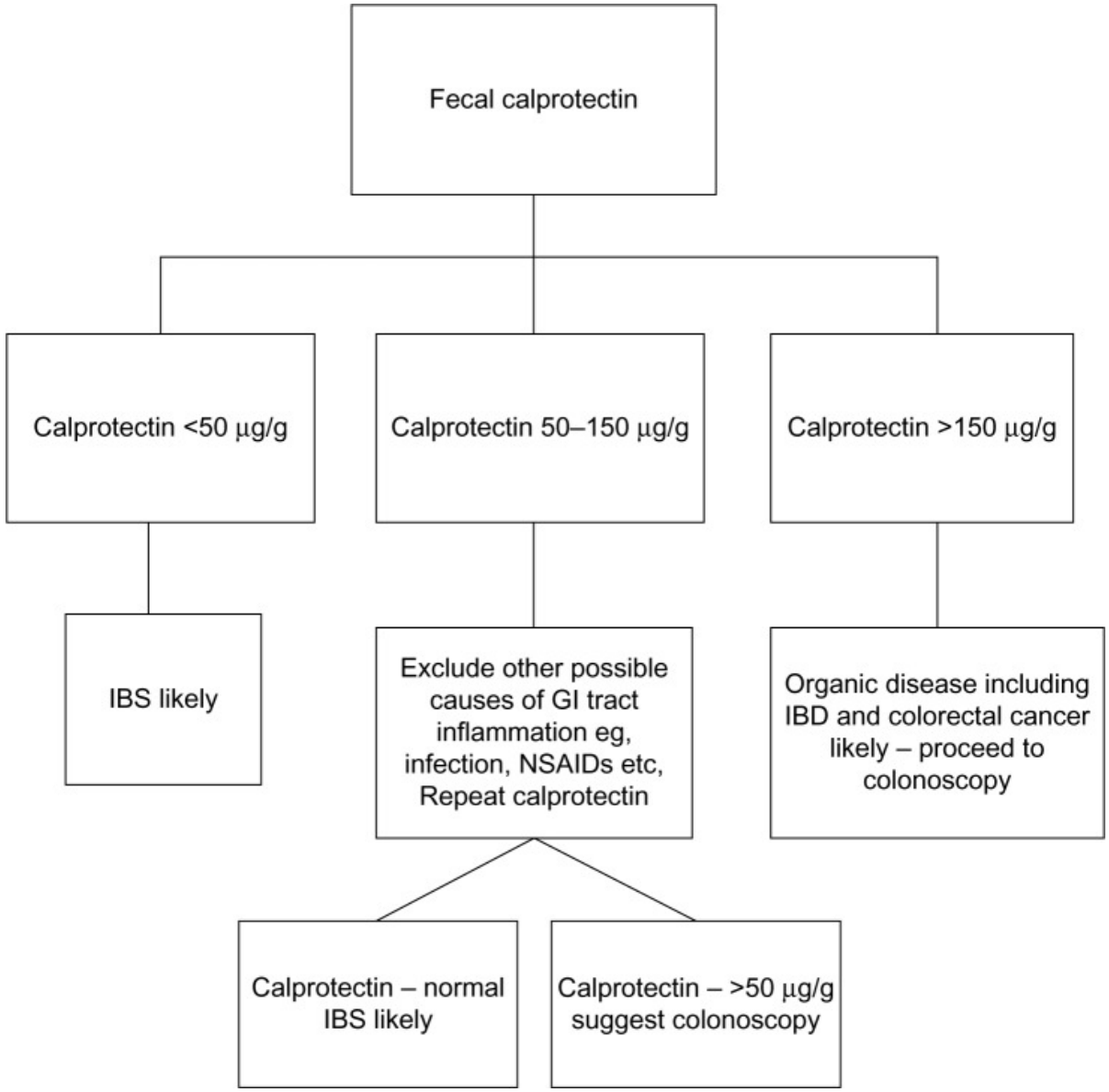
Inflammatory bowel disease

Inflammatory markers



Pang T et al, Front. Pediatr 2014

Inflammatory bowel disease



Walsham NE et al, Clin Exp Gastroenterol 2016

Inflammatory bowel disease

- Affect women of childbearing potential
- Associated with adverse pregnancy course and outcomes
- Disease activity at conception and during pregnancy associated with higher rates of spontaneous abortion, preterm delivery and low birth weight
- Disease activity increases thrombo-embolic events risk and emergency caesarean delivery
- Disease remission is a good prognostic factor for maintaining remission during pregnancy, child outcome

Drug	Pregnancy	Lactation	FDA category
Mesalazine	Low risk, avoid dibutyl phtlate coating	No contraindication	B
Sulfasalazine	Low risk, combine with increased dose folic acid, men: reversible infertility	Limited date	B
Corticosteroids*	Low risk, prednisone, prednisolone, methylprednisolone	No contraindication 4 hours delay	C
	Not recommended: dexamethasone, betamethasone		
Thiopurines	Low risk: azathioprine, 6-MP	Limited data	D
	6-TG: avoid if possible: limited data	6-TG: avoid if possible	
Anti-TNF	Low risk, small sized studies	Limited data	B
Methotrexate	Contraindicated for males and females	Contraindicated	X
	Stop 3–6 months before conception		
Thalidomide	Contraindicated	Contraindicated	X
Metronidazole	Low risk	Limited data	B
Ciprofloxacine	Limited data, avoid in first trimester	Limited data	C

Van der Woude CJ et al, Gut 2014

Diagnosis and management of functional symptoms in inflammatory bowel disease in remission

- Many inflammatory bowel disease patients in remission suffer from ongoing gastrointestinal symptoms that resemble those of irritable bowel syndrome and that hinder their quality of life
- The range of reported prevalences is quite wide (11%-64%), also in CD (12%-68%) and in UC (9%-60%) separately
- Pooled prevalence is 30.9%, 38.1% in CD and 27.8% in UC
- Microscopic inflammation in normal-appearing mucosa could persist after resolution of an acute flare and justify persistence of symptoms in spite of mucosal healing
- IBD induces hypersensitivity
- IBD induces mucosal permeability increment
- Microbiota disturbance plays a role

Teruel C et al, World J Gastrointest Pharmacol Ther 2016

Outline

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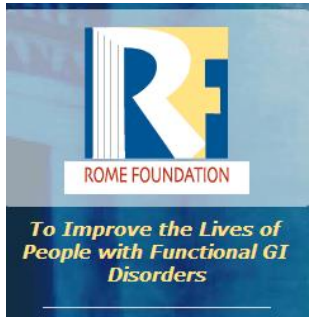
ROME III Questionnaire



- The Rome criteria are used to classify functional gastrointestinal disorders (FGIDs), in which symptoms cannot be explained by the presence of structural or tissue abnormality, based on clinical symptoms. Some examples of FGIDs include irritable bowel syndrome, functional dyspepsia, functional constipation, and functional heartburn

- *Red Flags*: identify patients that require additional exams to exclude organic causes

http://www.romecriteria.org/questionnaires/

GRAAL Study

- Methods: a simplified version of Rome III criteria was administred to the enrolled patients during the three visits in the three trimesters;
- Questionnaires were analyzed using the *Rome III Scoring system*
- Red Flags were reported separately

N° patients	I Trimester	II Trimester	III Trimester
Complete questionnaires	121/127 (95%)	107/127 (84%)	84/127 (66%)
Unspecified IBS	52 (43%)	42 (39%)	38 (45%)
Bloating/Constipation	5 (4%)	4 (4%)	2 (2%)

Risultati

Numero di pazienti	**1° Trimestre**	**2° Trimestre**	**3° Trimestre**
	n=121	**n=107**	**n=84**
Pirosi n (%)	1 (0.8)	7 (6.5)	5 (6)
Dolore toracico n (%)	1 (0.8)	1 (0.9)	0 (0)
Disfagia n (%)	0 (0)	0 (0)	0 (0)
Globo n (%)	0 (0)	0 (0)	0 (0)
Dispepsia n (%)	0 (0)	1 (0.9)	1 (1.2)
Distress post-prandiale n (%)	0 (0)	3 (2.8)	1 (1.2)
Epigastralgia n (%)	0 (0)	0 (0)	0 (0)
Aerofagia n (%)	6 (5)*	20 (18.7)*	14 (17)*

Risultati

Numero di pazienti	**1° Trimestre**	**2° Trimestre**	**3° Trimestre**
	n=121	**n=107**	**n=84**
Nausea cronica n (%)	2 (1.6)	2 (1.9)	5 (6)
Vomito funzionale n (%)	0 (0)	1 (0.9)	2 (2.4)
vomito ciclico n (%)	4 (3.3)	1 (0.9)	2 (2.4)
Borgorigmi n (%)	1 (0.8)	2 (1.9)	1 (1.2)
IBS n (%)	12 (10)	14 (13)	10 (12)
Gonfiore addominale n (%)	29 (24)	23 (21)	21 (25)
Stipsi n (%)	12 (10)	12 (11)	10 (12)
diarrea n (%)	0 (0)	3 (2.8)	1 (1.2)

Risultati

Numero di pazienti	**1° Trimestre n=121**	**2° Trimestre n=107**	**3° Trimestre n=84**
Unspecified BS n (%)	52 (43)	42 (39)	38 (45)
Sintomi defecatori n (%)	3 (2.5)	5 (4.7)	4 (4.8)
Proctorragia n (%)	3 (2.5)	6 (5.6)	4 (4.8)
Melena n (%)	13 (10)	17 (16)	17 (20)
Familiarità per K GI n (%)	5 (4)	5 (4.7)	7 (8)
Familiarità per IBD n (%)	3 (2.5)	4 (3.7)	2 (2.4)
Familiarità per celiachia n (%)	1 (0.8)	0 (0)	0 (0)

GRAAL Study

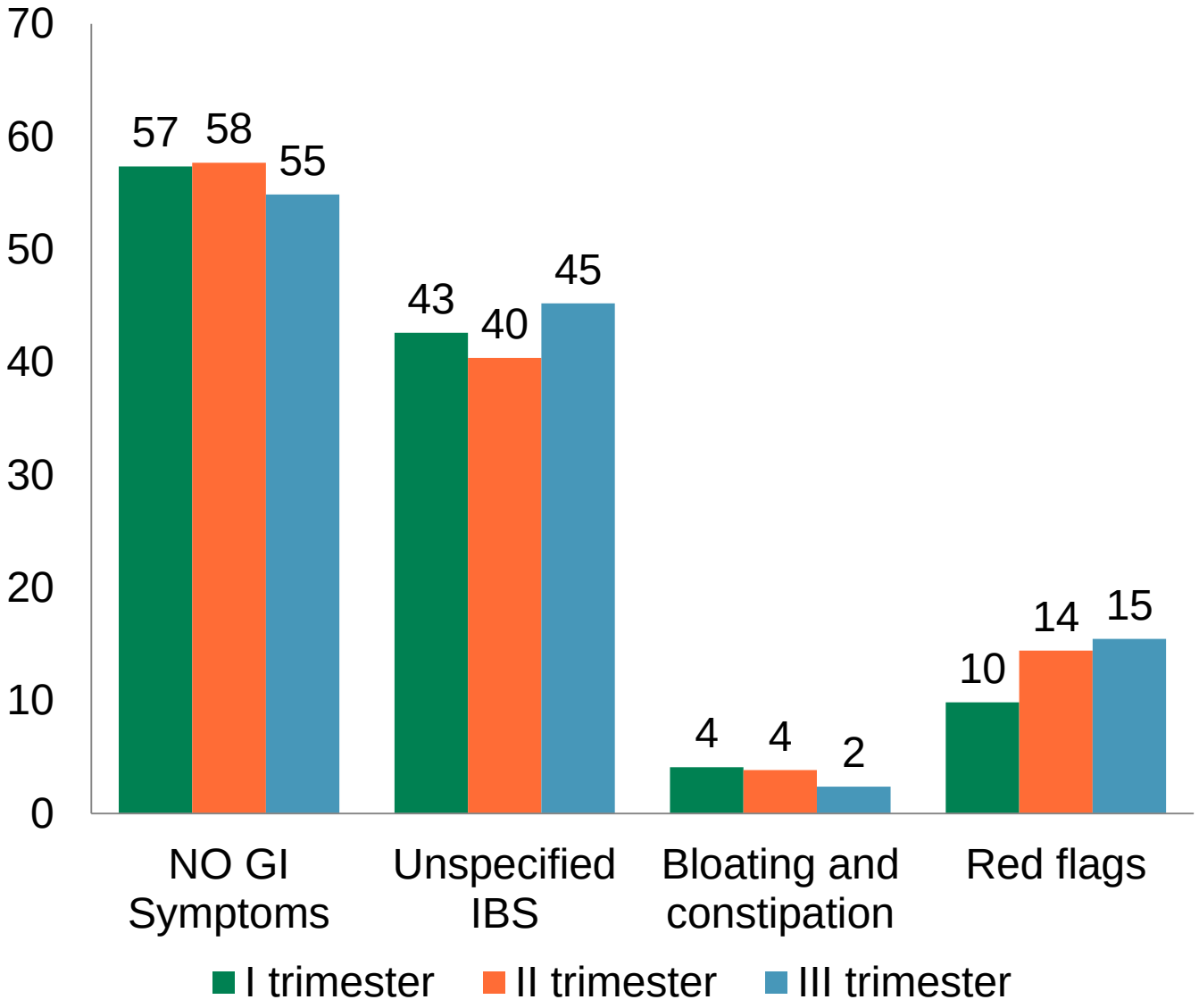
N° patients	I Trimester	II Trimester	III Trimester
Complete questionnaires	121/127 (95%)	107/127 (84%)	84/127 (66%)
Unspecified IBS	52 (43%)	42 (39%)	38 (45%)
Bloating/Constipation	5 (4%)	4 (4%)	2 (2%)
Red Flags	12 (8%)	15 (14%)	13 (16%)

GRAAL Study

Red Flags

N° patients	I Trimester	II Trimester		III Trimester
Proctorrhagia n (%)	3 (2.5)	6 (5.6)	p=NS	4 (4.8)
Black Stools n (%)	13 (10)	17 (16)	p=NS	17 (20)
GI Cancer positive Family history, n (%)	5 (4)	5 (4.7)	p=NS	7 (8)
IBD positive Family history, n (%)	3 (2.5)	4 (3.7)	p=NS	2 (2.4)
Celiac disease positive Family history, n (%)	1 (0.8)	0 (0)	p=NS	0 (0)

GRAAL Study


70
60
50
40
30
20
10
0
57
58
55
43
40
45
4
4
2
10
14
15
NO GI Symptoms
Unspecified IBS
Bloating and constipation
Red flags
I trimester
II trimester
III trimester

GRAAL Study

Unspecified IBS	I trimester (n=52/122)	II trimester (n=42/104)	III trimester (n=38/84)
Age, mean (SD)	33.8 (3.5)	34.3 (3.6)	33.5 (3.6)
WBC, mean (SD)	8.0 (1.6)	9.22 (1.89)	9.1 (1.9)
Hb, mean (SD)	12.3 (1)	11.5 (0.8)	11.7 (0.97)
Mediterranean Diet Score >9, %	21.4%	15%	20%
Smoking, %	4.3%	3.3%	0%
Paf, mean (SD)	6 (4.7)	5.8 (5.5)	5.9 (5.2)
Baff, mean (SD)	1.6 (1.2)	1.6 (1.2)	1.7 (1.4)
Adiponectin, mean (SD)	11393 (4572)	8347 (3158)	8734 (4383)
Omocistein, mean (SD)	6.2 (1.4)	6.7 (1.3)	7.2 (1.9)
IL-6, mean (SD)	7.7 (27)	9 (33.5)	4.7 (6.1)
C3, mean (SD)	1.37 (0.19)	1.33 (0.19)	1.39 (0.21)
Fecal calprotectin, mean (SD)	33.4 (15.5)	30 (11.2)	34.3 (7.3)

Outline

1. Gastrointestinal manifestations in pregnancy
2. Irritable bowel syndrome/Inflammatory bowel disease
3. Rome III criteria and GRAAL study
4. Conclusions

Conclusions

- During pregnancy up to 50% of women complain of some degree of gastrointestinal symptoms, mainly nausea and vomiting, constipation and gastro-esophageal reflux;
- Most of these manifestations are mild and self limiting but affect quality of life and may require treatment;
- Few treatments and safety data are available, and most pregnant women seek help in unproven alternative medicine;
- IBS represents the most common gastrointestinal condition (40-43%), with new potential etiologies beyond the functional status, few data are available in pregnancy;
- IBD are more rare inflammatory diseases but may affect pregnancy outcome;
- Red flags signs and calprotectin may help

Conclusions

- In our prospective study on 127 pregnant women, 40% suffered from unspecified IBS, with no differences in the three trimesters;
- No differences were observed between the healthy and IBS women in demographic and serological markers;
- There was no correlation between IBS symptoms and pregnancy outcomes;
- More studies are needed to assess the relationship between IBS and pregnancy
- Analysis of dietary and immune factors is in progress

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Thanks for your attention!

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