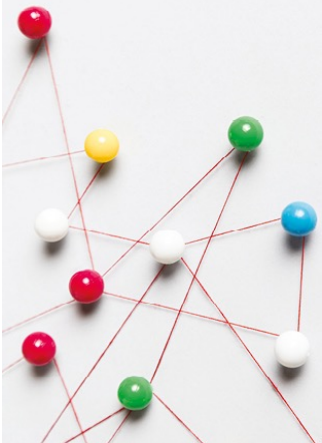


Malattia celiaca e problematiche femminili

Prof.ssa Nicoletta Di Simone, Humanitas
University, Milano



Clinical Gastroenterology and Hepatology 2019;17:1954-1968

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Sex Difference in Celiac Disease in Undiagnosed Populations: A Systematic Review and Meta-analysis

Claire L. Jansson-Knodell,* Isabel A. Hujoel,* Colin P. West,^{†,§} Veena Taneja,^{||}
Larry J. Prokop,[¶] Alberto Rubio-Tapia,[#] and Joseph A. Murray[#]



Data from 291,969 study participants

Prevalence of undetected celiac disease in female participants was 0.589% (95% CI, 0.549%-0.629%) and in male participants was 0.415% (95% CI, 0.343%-0.487%)

Higher risk for celiac disease in women than men in an undiagnosed populations (identified through general population screening).



The increased risk for celiac disease among girls and women should be considered for screening, diagnosis, and management strategies.

11° CONVEGNO NAZIONALE AIC

Roma • 10 novembre 2023

AiC  Associazione
Italiana
Celiachia

45
anni
1979-2024



Celiac disease through the stages of woman's fertile life

Table 1 | Extraintestinal manifestations of coeliac disease

Manifestation	Prevalence	Pathophysiology	Testing and treatment
Anaemia	Common	Nutritional deficiencies: iron most frequently followed by folate and vitamin B ₁₂ Chronic inflammation	Regular testing of haemoglobin and vitamin status recommended
Reduced bone density	Common	Nutritional, inflammatory, autoimmune	BMD testing recommended within 1 year of diagnosis
Arthritis	Common	Inflammatory and/or autoimmune	Evaluation of symptomatic individuals
Dermatitis herpetiformis	Uncommon	Autoimmune: crossreaction of TG2 antibodies with TG3 in skin	Skin biopsy of suspected disease, adjunctive treatment with dapsone
Eczema or psoriasis	Uncommon	Inflammatory	Consider coeliac disease in severe psoriasis
Gluten ataxia	Rare	Autoimmune	Coeliac disease testing in idiopathic ataxia
Autism	Not clearly associated	Unknown	Coeliac disease testing in ASD is reasonable
Schizophrenia	Not clearly associated	Unknown	Coeliac disease testing not typically recommended
Peripheral neuropathy	Common	Autoimmune, inflammatory	Coeliac disease testing in unexplained neuropathy
Short stature	Common in paediatric populations	Nutritional, hormonal, inflammatory	Coeliac disease testing in growth delay
Delayed puberty	Uncommon	Nutritional, hormonal, inflammatory	Coeliac disease testing in affected individuals
Hepatitis	Common	Inflammatory, autoimmune	LFT testing in patients with coeliac disease, coeliac disease testing in unexplained liver disease
Cardiovascular manifestations	Not clearly associated	Nutritional, inflammatory	None
Splenic manifestations	Uncommon	Autoimmune, inflammatory, haemodynamic	Consider vaccination against influenza, pneumococcus
Pulmonary manifestations	Rare	Autoimmune	None
Renal manifestations	Rare	Autoimmune	None
Pancreatic manifestations	Uncommon	Obstructive, inflammatory	Pancreatic exocrine testing in nonresponsive coeliac disease
Reproductive manifestations including impaired fertility	Uncommon	Nutritional, inflammatory, autoimmune	Coeliac disease testing in unexplained infertility
Dental	Uncommon	Nutritional, inflammatory	Coeliac disease testing in dental enamel defects

Abbreviations: ASD, autism spectrum disorder; BMD, bone mineral density; TG2, tissue transglutaminase 2; TG3, transglutaminase 3; LFT, liver function tests.

Coeliac disease and adolescence

Coeliac disease is present in up to 8.3% of children evaluated for short stature → Decreases in serum levels of insulin-like growth factor 1 and insulin-like growth factor binding protein

Delayed onset of puberty due to hypogonadism (case reports)

Delayed menarche has been documented in girls with coeliac disease, but not in those on a gluten-free diet (case reports)

Celiac disease and adolescence

Clinical Research Report

 *Journal of*
**INTERNATIONAL
MEDICAL RESEARCH**

Journal of International Medical Research
0(0) 1–8
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Onset of menarche is not delayed in Slovenian patients with celiac disease

**Dušanka Mičetić-Turk¹, Veljko Vlasisavljević²,
Eva Turk¹ and Maja Šikić Pogačar¹**

2019

The study included 145 patients with CD (age, 15–51 years) and 162 healthy women (age, 18–55 years).

The age at menarche in patients with CD (treated or untreated) is 12.7 years, which is comparable with that in healthy women

	Age at diagnosis (yr)	Menarcheal age (yr)
Group A (117)	7.4±4.1	12.4±1.4 ^b
Group A mothers (117)	-	12.1±1.3 ^b
Group B (94)	20.7±5.8 ^a	12.4±1.4 ^b
Group B mothers (94)	-	12.3±1.3 ^b
Controls (280)	-	12.2±1.1

^ap<0.001 compared to Group A age at diagnosis. ^bNo significant differences compared to the patients of the other group, to the respective mothers and to healthy controls.

This study covers a population of 94 menarcheal adolescents with untreated CD, whose MA was compared with that of 3 control populations:

- 117 early-treated CD girls
- their non-celiac mothers
- 280 healthy adolescents

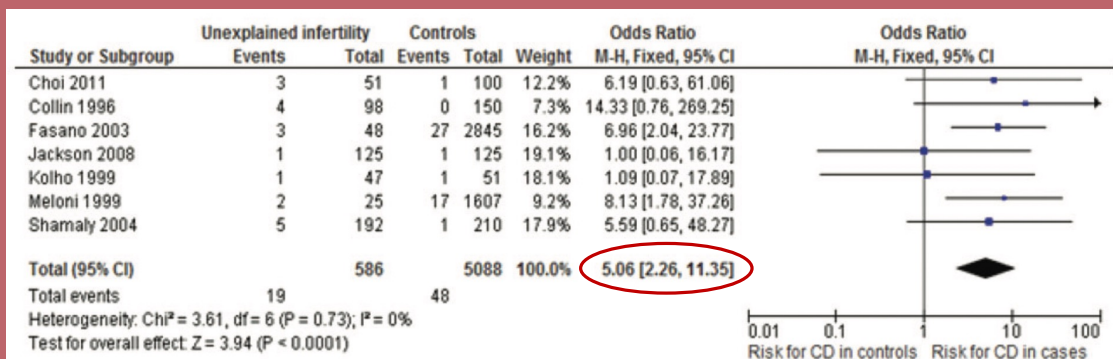
Celiac disease and fertility

Approach to the Patient With Infertility

- Women desiring pregnancy who have not conceived after 12 months of unprotected intercourse or donor insemination should be offered an infertility evaluation
- **Earlier evaluation is recommended for women older than 35 years who have not conceived for 6 months, and more immediate evaluation is warranted for women older than 40 years.**
- Fertility evaluation is also recommended for women with oligomenorrhea or amenorrhea, known or suspected uterine, tubal, or peritoneal disease (including stage III or IV endometriosis), and male partners with known or suspected male factor infertility

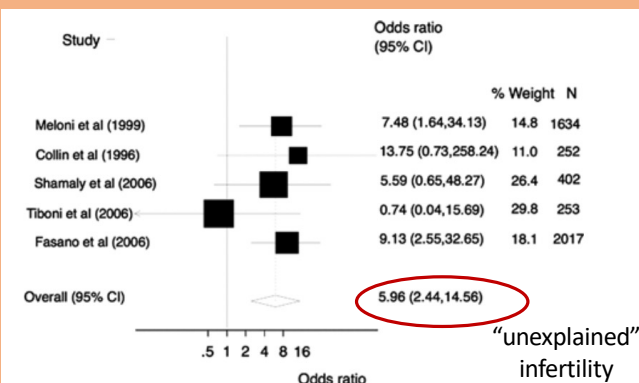
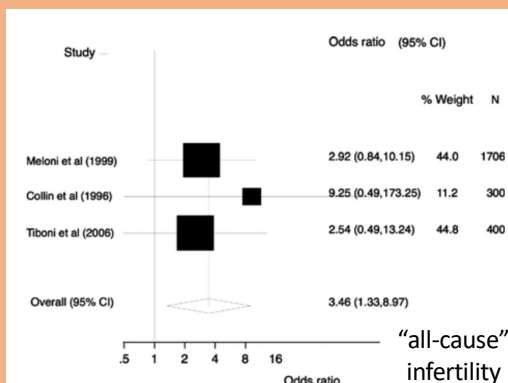
JAMA, 2021

Celiac disease in patients with infertility



In patients with unexplained infertility, the risk of celiac disease is 5.82 (95% CI 2.30 – 14.74)

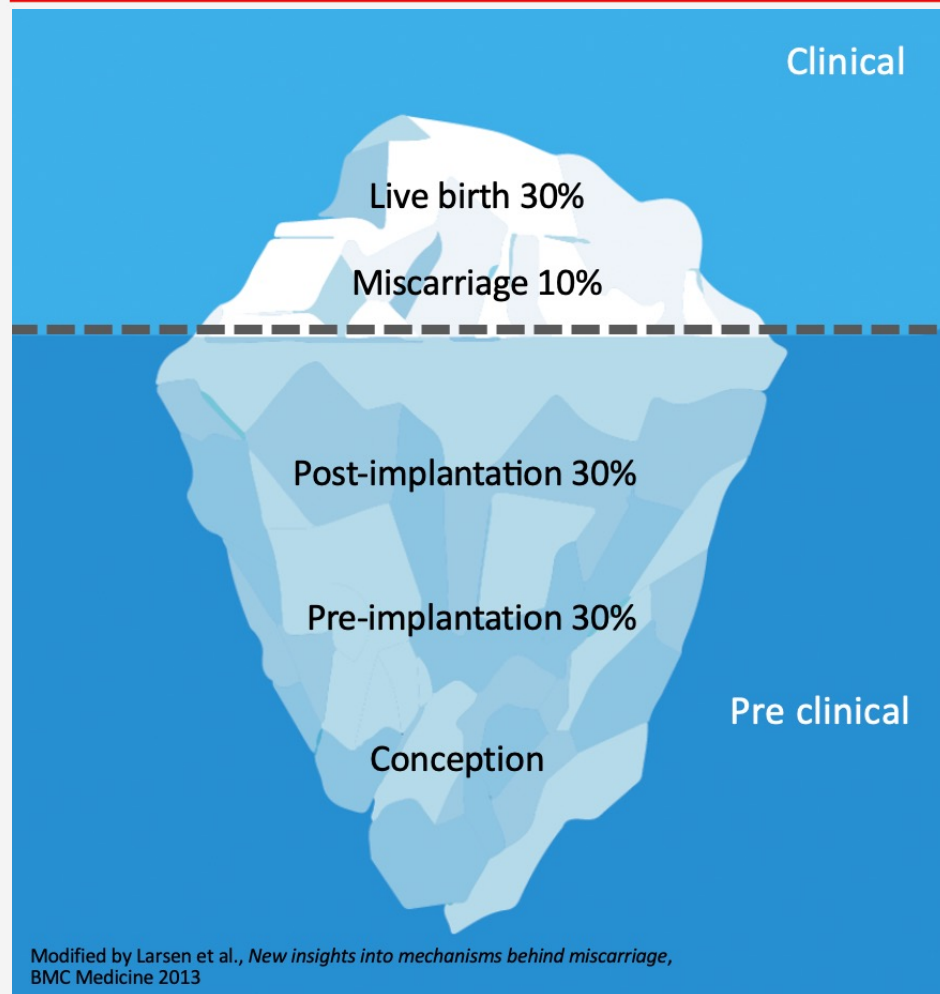
Tersigni et al. Hum Reprod Update. 2014



Women with infertility had 3.5 times higher odds of having CeD in comparison with control population (OR = 3.5; 95% CI, 1.3-9; $P < 0.01$). Similarly, women with "unexplained infertility" had 6 times higher odds of having CeD than controls (OR = 6; 95% CI, 2.4-14.6).

Singh et al. J Clin Gastroenterol. 2016

What about the obstetric outcome in patients
with celiac disease?



The pregnancy loss iceberg

Miscarriage complicates 15-20% of clinically known pregnancies

80% of miscarriages occur in the first 12 weeks of gestation

Recurrent pregnancy loss (> 2 miscarriages) affects about 5% of couples trying to conceive globally (50% unexplained!)

Celiac disease and recurrent pregnancy loss

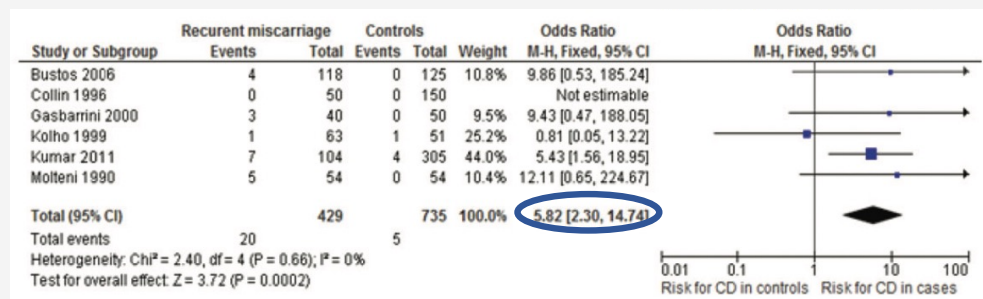
human reproduction update

2014

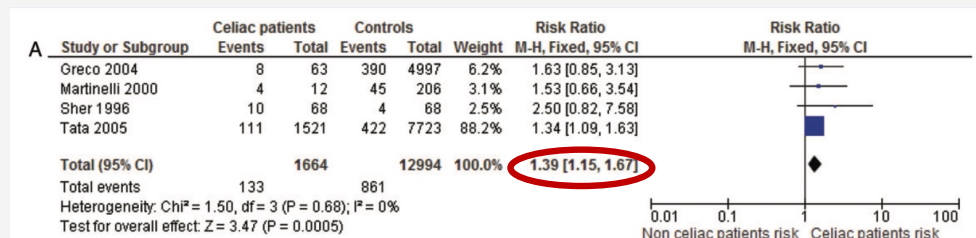
Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms

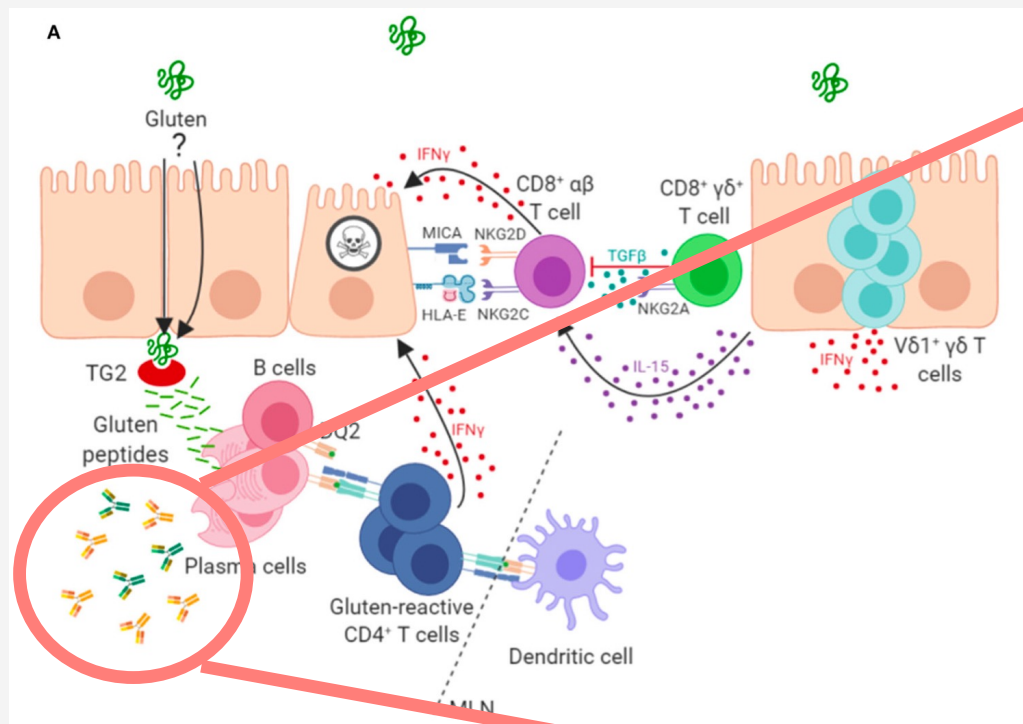
Chiara Tersigni¹, Roberta Castellani¹, Chiara de Waure²,
Andrea Fattorossi¹, Marco De Spirito³, Antonio Gasbarrini⁴,
Giovanni Scambia¹, and Nicoletta Di Simone^{1,*}

Risk of CD in patient with history of recurrent miscarriage

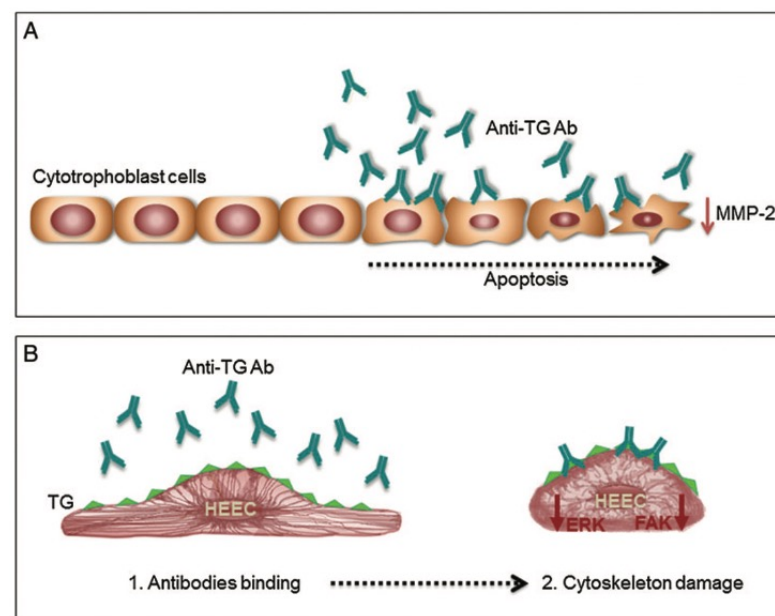


Risk of miscarriage in patient with CD





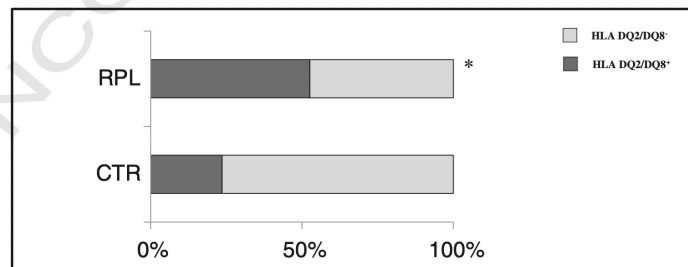
Fetal side



Maternal side



Recurrent pregnancy loss and HLA DQ2/DQ8



Prevalence of HLA-DQ2/DQ8 positivity in Recurrent Pregnancy Loss (RPL) and control (CTR) women.
*Statistical significance: $p < 0.05$.

	CTR (n=55)	RPL (n=97)	P value
HLA DQ2/DQ8 ⁺ n (%)	13 (23.6%)	51 (52.6%)	<0.01

Fig. 1.

Analysis of association between anti-thyroid, -cardiolipin, -nuclear, $\beta 2$ glycoprotein 1, -prothrombin antibody positivity, and HLA DQ2/DQ8 status.

	HLA DQ2/DQ8 positive	HLA DQ2/DQ8 negative	p
Anti-thyroid antibody			
Positive	15 (31.9%)	11 (23.9%)	0.39
Negative	32 (68.1%)	35 (76.1%)	
Anti-nuclear antibody			
Positive	26 (55.3%)	10 (23.3%)	<0.01*
Negative	21 (44.7%)	33 (76.7%)	
Anti-cardiolipin antibody			
Positive	4 (9.3%)	3 (7.3%)	1.00 [§]
Negative	39 (90.7%)	38 (92.7%)	
Anti- $\beta 2$ glycoprotein 1 Antibody			
Positive	5 (12.2%)	2 (5.1%)	0.43 [§]
Negative	36 (87.8%)	37 (94.9%)	
Anti-prothrombin antibody			
Positive	1 (2.7%)	5 (14.3%)	0.10 [§]
Negative	36 (97.3%)	30 (85.7%)	

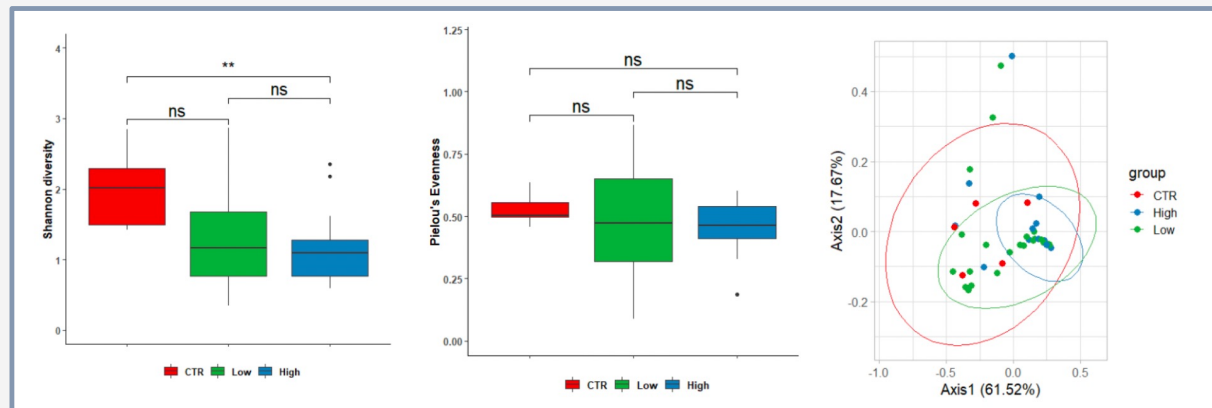
Article

Celiac Disease Predisposition and Genital Tract Microbiota in Women Affected by Recurrent Pregnancy Loss

Luca Masucci ^{1,2,†} , Silvia D'Ippolito ^{3,*,†} , Flavio De Maio ² , Gianluca Quaranta ², Roberta Mazzarella ³, Delia Mercedes Bianco ¹, Roberta Castellani ³, Annalisa Inversetti ^{4,5}, Maurizio Sanguinetti ^{1,2} , Antonio Gasbarrini ^{6,7}, Giovanni Scambia ^{3,8} and Nicoletta Di Simone ^{4,5}

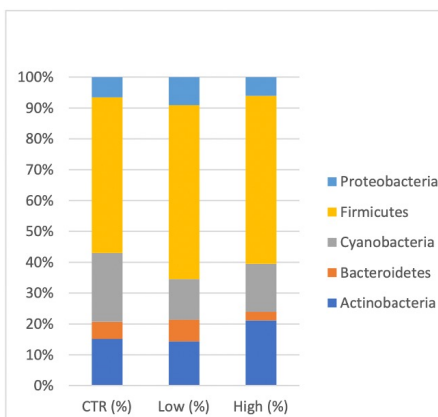
Endometrial and vaginal microbiota were analyzed in 40 RPL patients of whom 15 were HLA-DQ2/DQ8 positive and 25 were HLA DQ2/DQ8 negative, in order to investigate the pathogenic role of celiac disease predisposition on microbiota.



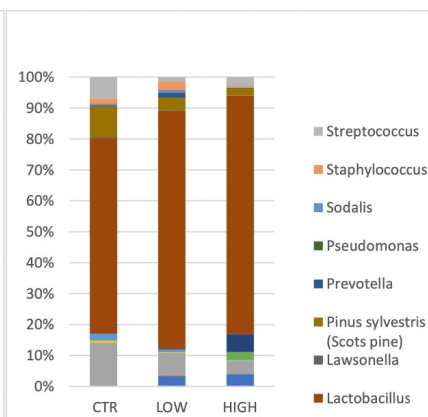


PERMANOVA statistical test showed a significant change between control (CTR) and HLA-DQ2/DQ8 positive-RPL women in ($p = 0.037$, $R^2 = 0.109$) in **endometrial sample**.

Phylum level: Relative abundance detected in **endometrial samples**.

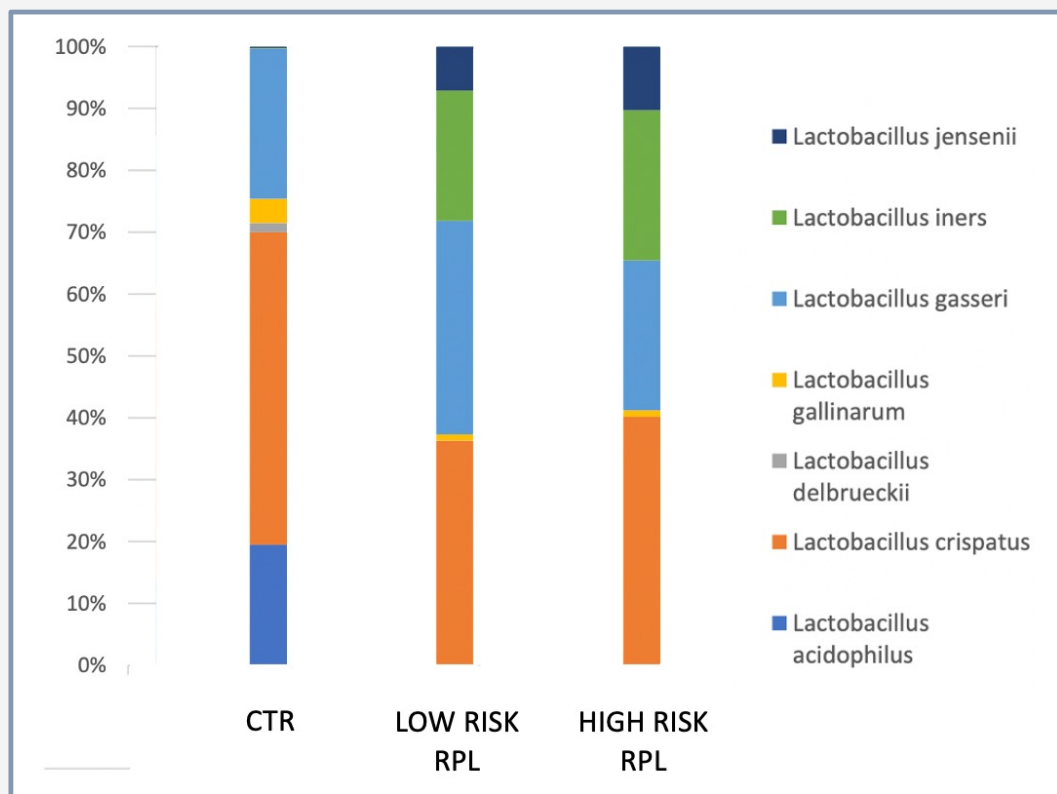


Genus level: Relative abundance detected in **endometrial samples**.



In the endometrium, *Bacteroidetes* and *Proteobacteria* were equally distributed among the three groups, while *Firmicutes* were more prevalent in the HLA-DQ2/DQ8 negative subgroup (86.38%) compared to healthy women ($\approx 67.5\%$) and the HLA-DQ2/DQ8 positive RPL subgroup (65.2%).

Differences in Lactobacillus Species



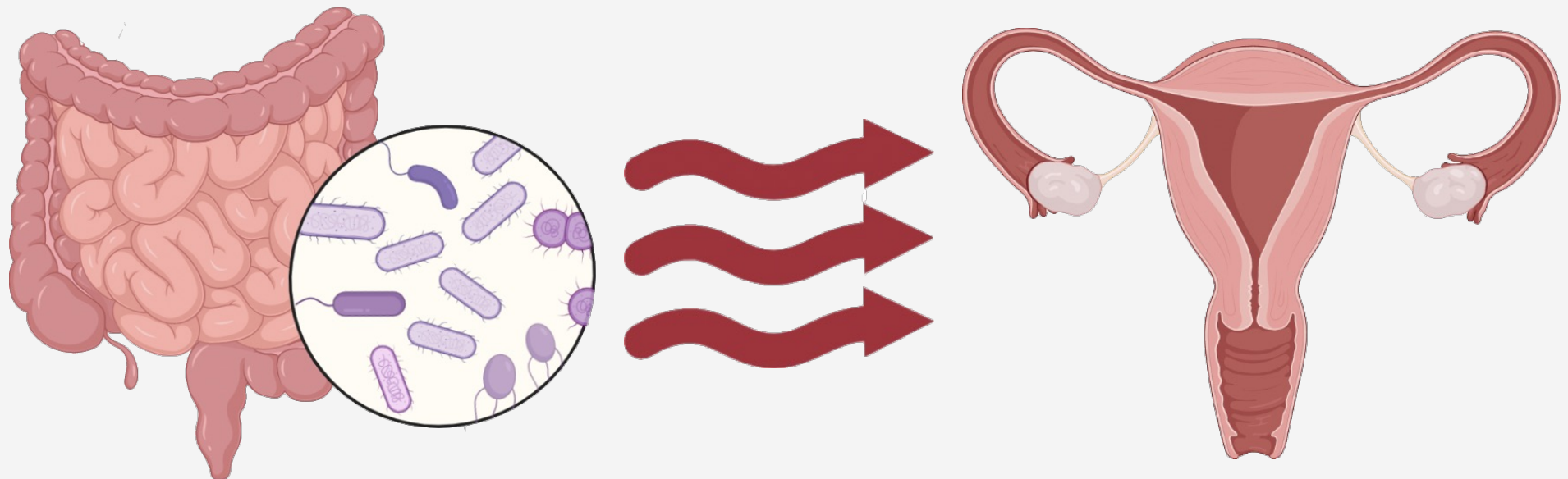
Endometrial samples

Main findings:

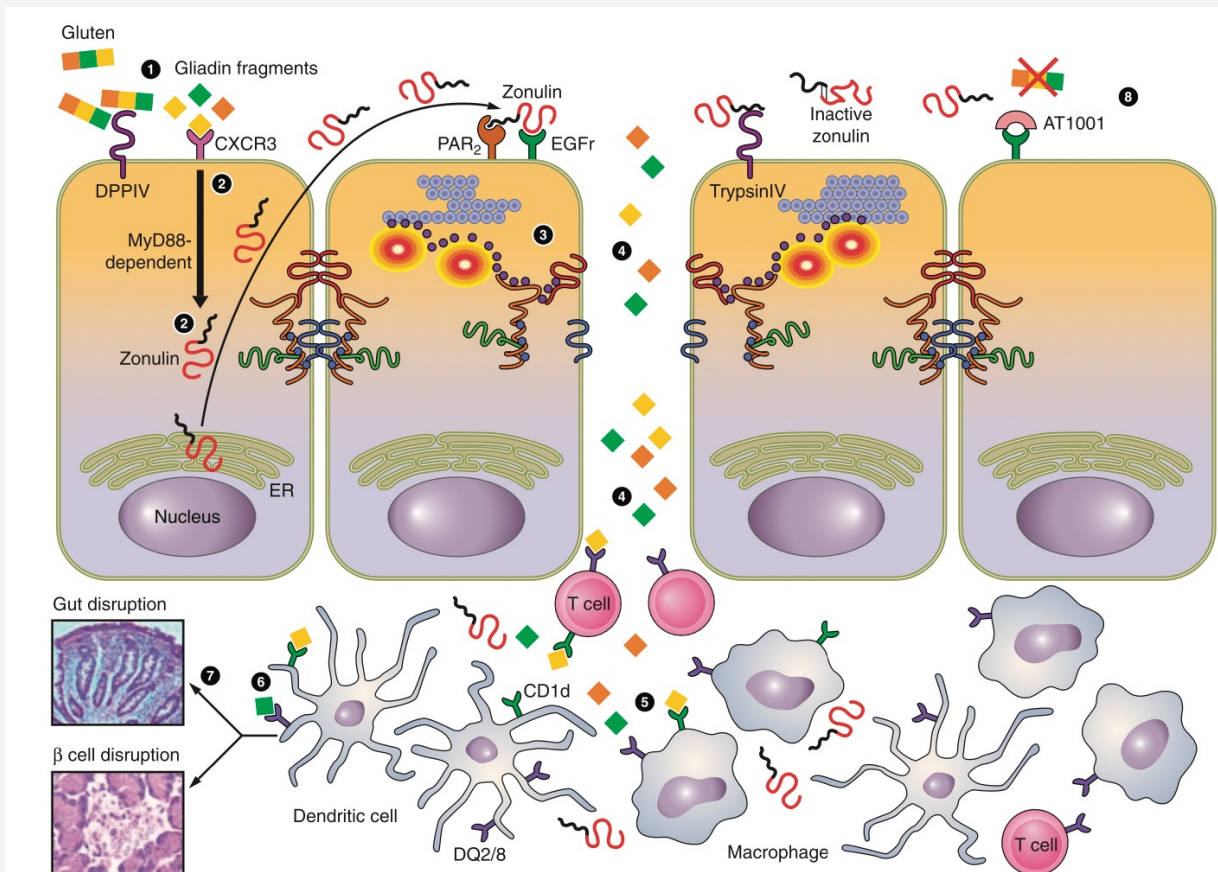
- healthy control endometrial samples were mainly constituted by *L. acidophilus*, *L. crispatus*, and *L. gasseri*
- both subgroups of RPL women (HLA-DQ2/DQ8 positive and negative), *L. acidophilus* was not detected and *L. iners* was equally distributed
- very low value of the *L. iners* relative abundance was detected in the control group

Nutrients 2023

Gut and Endometrium: witch connection?

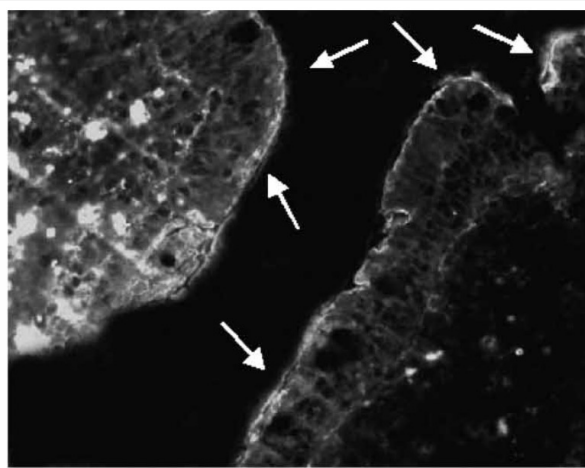


Intestinal permeability in celiac disease

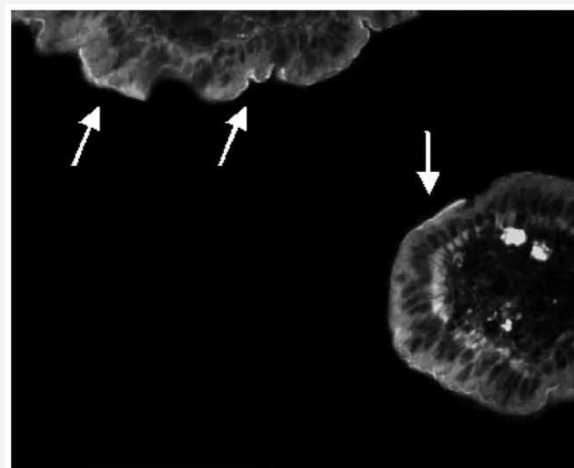


Fasano et al. *Physiol Rev.* 2011

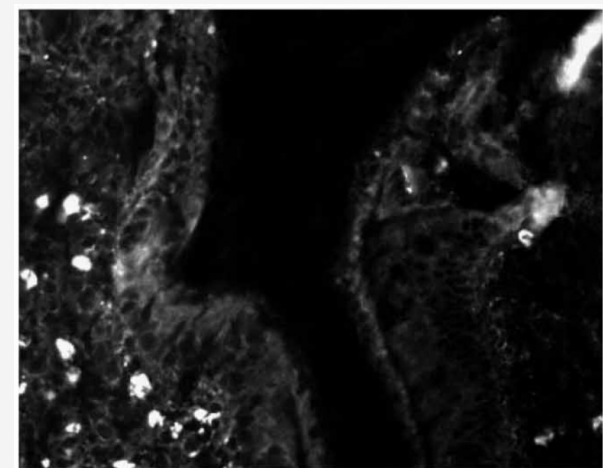
Intestinal permeability in celiac disease: zonulin expression *in vivo*



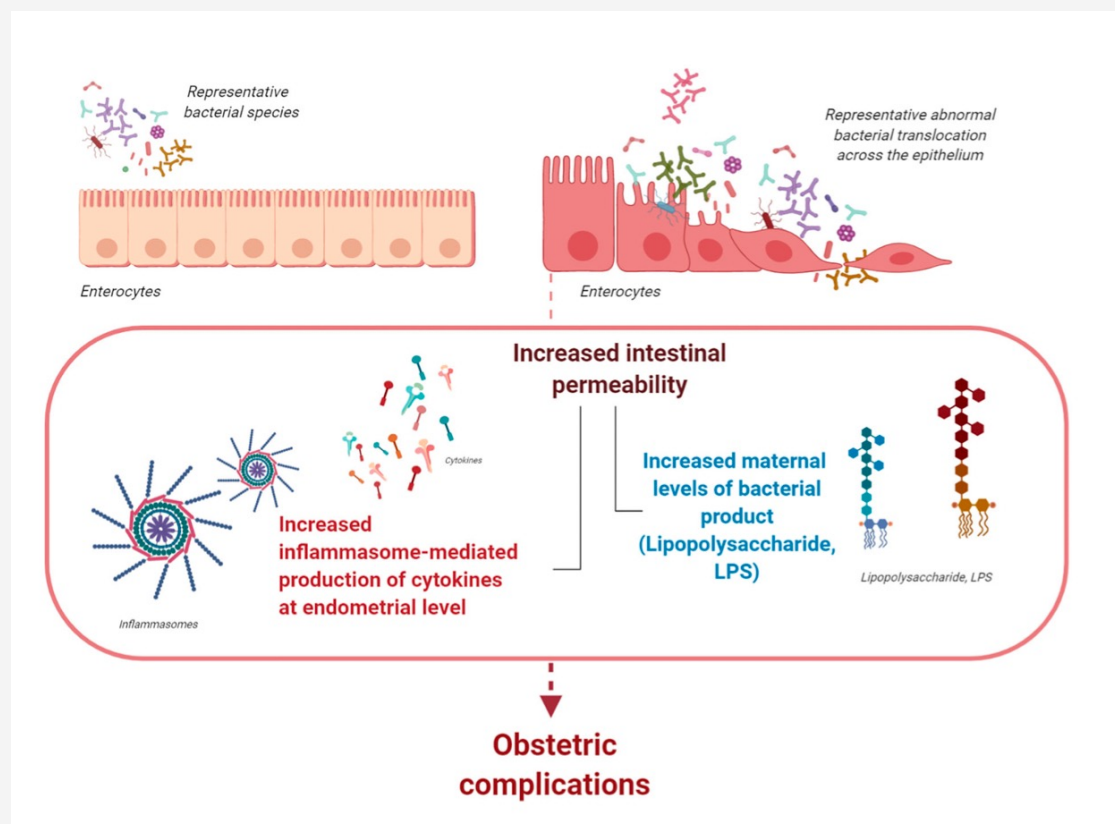
CD patients exposed to gliadin showing a homogeneous staining on the mucosal surface



Non – CD controls exposed to gliadin also showing mucosal surface staining; however, the zonulin binding appears patchy



Non – CD controls not exposed



Recent Insights on the Maternal Microbiota: Impact on Pregnancy Outcomes

Nicoletta Di Simone^{1,2*}, Amparo Santamaria Ortiz³, Monia Specchia¹, Chiara Tersigni², Paola Villa^{1,2}, Antonio Gasbarrini⁴, Giovanni Scambia^{1,2} and Silvia D'Ippolito²

Celiac predisposition and endometrial inflammation

Untreated women with unexplained RPL, HLA-DQ2/DQ8 positive (n22) and unexplained RPL, HLA-DQ2/DQ8 negative (n22; controls)

	RPL (n=22)	Controls (n=22)	P
LPS	980.0 (716.0-1134.0)	730.5 (12.4-864.2)	<0.00001
Zonulin	5.3 (2.9-8.7)	3.675 (1.3-8.9)	0.14

LPS: lipopolysaccharides; RPL: recurrent pregnancy loss.

Plasma

	RPL (n=22)	Controls (n=22)	P
LPS	895.3 (655.5-1718.0)	484.5 (426.0-799.0)	< 0.00001
NALP-3	0.6 (0.3-1.6)	0.4 (0.3-0.7)	< 0.01
Caspase-1	1.3 (0.7-319.6)	0.7 (0.0-1.0)	< 0.00001
IL-1 β	214.2 (15.6-569.5)	39.8 (9.7-254.6)	< 0.05
IL-18	305.8 (96.7-773.3)	94.4 (44.2-221.8)	<0.00001

LPS: lipopolysaccharides; NALP-3: Nod-like receptor family pyrin domain containing 3; RPL: recurrent pregnancy loss.

Endometrial tissue

Under review

RPL women positive for **HLA-DQ2/DQ8 haplotype** show **increased circulating and endometrial levels of LPS and endometrial inflammasome NALP-3 over-activation.**

Celiac disease predisposition and endometrial inflammation

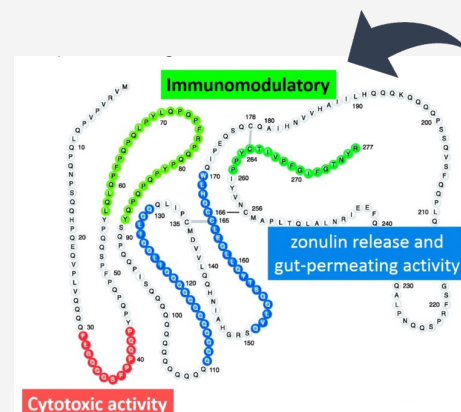
Under review

	RPL pre-treatment (n=22)	RPL post-treatment (n=22)	P
LPS	980.0 (716.0-1134.0)	631.5 (441.0-855.0)	<0.0001
Zonulin	5.3 (2.9-8.7)	3.9 (0.5-6.7)	< 0.05

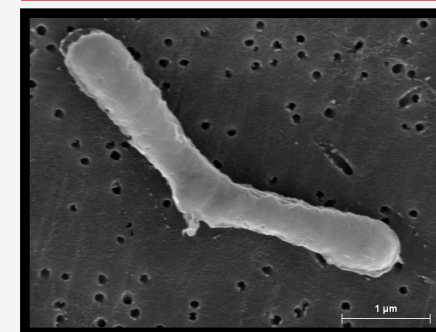
Serum levels of lipopolysaccharides and zonulin before and after 3 months of oral administration of Bifidobacterium longum ES1.

	RPL pre-treatment (n=22)	RPL post-treatment (n=22)	P
LPS	895.3 (655.5-1718.0)	671.1 (493.0-1723.0)	< 0.001
NALP-3	0.6 (0.3-1.6)	0.4 (0.3-0.8)	< 0.05
Caspase-1	1.3 (0.7-319.6)	0.8 (0.5-1.8)	< 0.00001
IL-1 β	214.2 (15.6-569.5)	74.8 (4.2-336.7)	< 0.01
IL-18	305.8 (96.7-773.3)	174.5 (33.2-358.9)	< 0.01

Levels of lipopolysaccharides, NALP-3, Caspase-1, IL-1 β and IL-18 in **endometrial fluids** from women with recurrent pregnancy loss before and after 3 months of oral administration of Bifidobacterium longum ES1

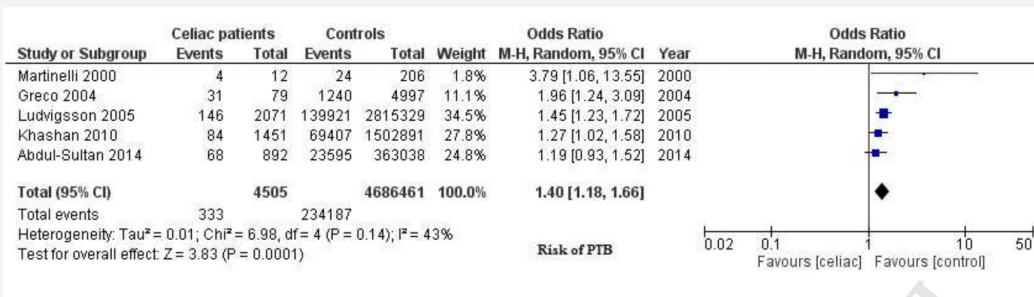


Alfa-gliadin degradation by Bifidobacterium longum ES1



RPL women positive for **HLA-DQ2/DQ8 haplotype** show increased circulating and endometrial levels of LPS and **endometrial inflammasome** NALP-3 over-activation. Oral administration of Bifidobacterium longum ES1 can reduce gut permeability, decrease serum levels of LPS and, contextually, improve endometrial inflammation in this specific subset of RPL women

Celiac disease and pregnancy



Women with celiac disease (both treated and untreated) had a significantly higher risk of developing **PTB, IUGR, LBW and SGA**, while no statistically significant difference was found in the incidence of preeclampsia



The risk of PTB was still significantly higher both in subgroup analysis of only diagnosed and treated celiac disease women (OR 1.26, 95% CI 1.06 to 1.48) and in subgroup analysis of only undiagnosed and untreated celiac disease women (OR 2.50, 95% CI 1.06 to 5.87).



Celiac disease and menopause

QUICK GUIDE TO KEY MENOPAUSE TERMS

MENOPAUSE

the permanent cessation of menstruation resulting from loss of ovarian follicular activity: may be natural or induced

TYPES OF MENOPAUSE

NATURAL

recognized to have occurred when a woman has had 12 consecutive months without periods (amenorrhea) due loss of ovarian follicular activity for which no other obvious pathological or physiological cause is present and occurs on average at the age of 51 years. Menopause occurs with the final menstrual period and thus is known with certainty only in retrospect one year after the event.

INDUCED

the cessation of menstruation which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g. by chemotherapy or radiation). Surgical menopause can be timed precisely.

PREMATURE OR EARLY

menopause occurring much earlier than the average age of 51 years. Thus, menopause before the age of 40 is commonly referred to as premature menopause, although primary ovarian insufficiency (POI) is currently considered to be a better term to denote the loss of ovarian function, as it does not specify definitive failure. Menopause that occurs between 40 and 45 years is termed early menopause.

STAGES OF MENOPAUSE

PREMENOPAUSE

the entire reproductive period from menarche to the final menstrual period

PERIMENOPAUSE

includes the period of time beginning with the first clinical, biological and endocrinological features of the approaching menopause, including vasomotor symptoms and menstrual irregularity, and ends 12 months after the last menstrual period

MENOPAUSAL TRANSITION

the time before the final menstrual period, when variability in the menstrual cycle usually is increased

POSTMENOPAUSE

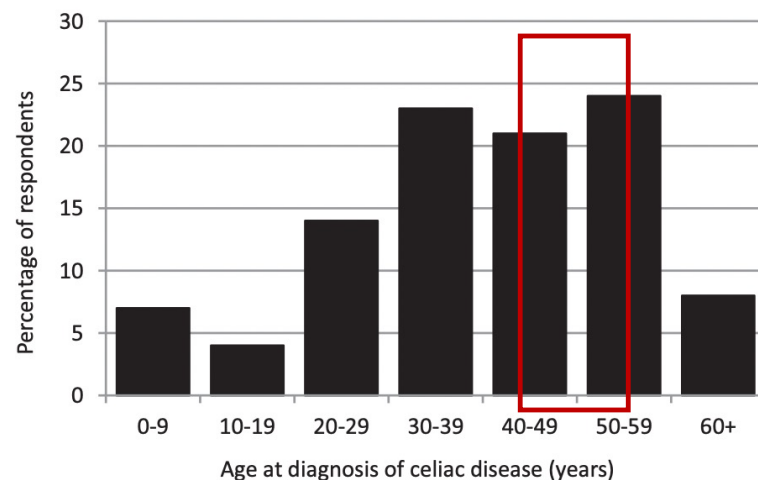
the time dating from the menopause



Infographic designed by Dr Margaret Rees & Dr Claire Hardy



Celiac disease and menopause



Distribution of age at diagnosis of the respondents with celiac disease

	Final Menstrual Period (FMP)							
Stages:	-5	-4	-3	-2	-1	0	+1	+2
Terminology:	Reproductive			Menopausal Transition			Postmenopause	
	Early	Peak	Late	Early	Late*		Early*	Late
				Perimenopause				
Duration of Stage:	variable			variable		a 1 yr Amen x 12 mos	b 4 yrs	until demise
Menstrual Cycles:	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)		none	
Endocrine:	normal FSH		↑ FSH	↑ FSH			↑ FSH	

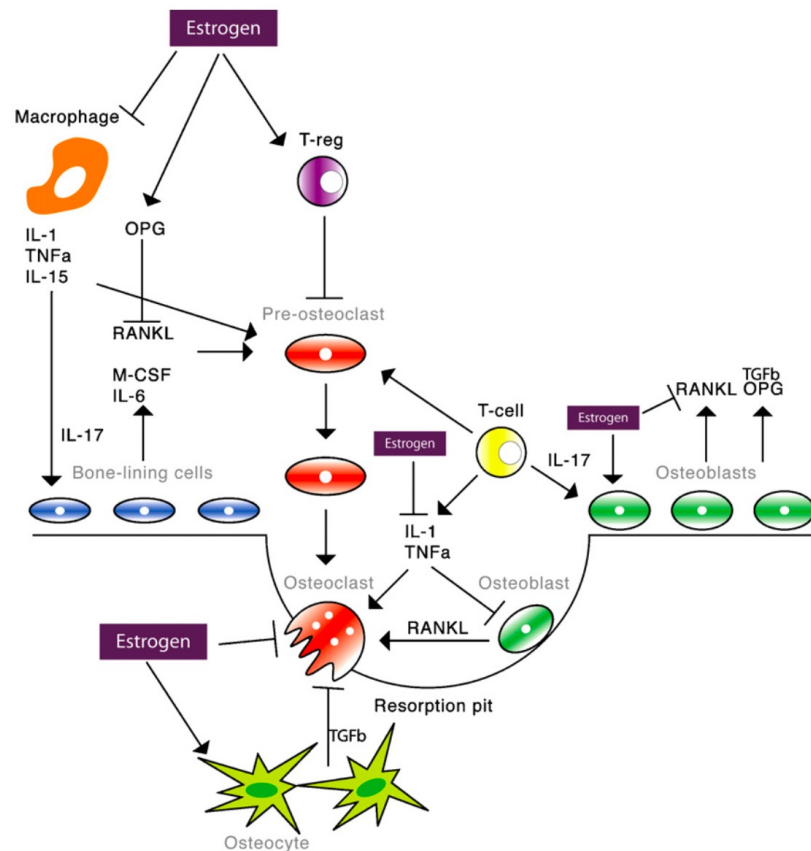
*Stages most likely to be characterized by vasomotor symptoms

↑ = elevated

*Stages most likely to be characterized by vasomotor symptoms ↑ = elevated

Stages of Reproductive Aging Workshop (STRAW)

Estrogen's action on bone health



Islander et al. Mol Cell Endocrinol. 2011

Table 1 | Prevalence of osteoporotic BMD in women with fracture

Study	n	T (years)	Site of BMD measurement	Osteoporosis prevalence ^a
NORA ¹⁴	149,524	1	Peripheral	18% of women aged >50 years with osteoporotic fractures ^b
Rotterdam ¹⁵	14,613	10.7	Femoral neck	21% of women aged >45 years with non-vertebral fracture
Dubbo ¹⁷	2,320	>15	Femoral neck	11–20% of fractures were attributable to osteoporotic BMD in women aged >60 years
Aarhus ¹⁶	556	1	Hip or spine	23% of women aged >50 years with any fracture

Reid et al. Nat Rev Endocrinol. 2020

Celiac disease and osteoporosis

Characteristic	CD group	Non-CD group	p-Value
Number	131	102	
Age (range) (years)	50.7 (18–89)	59.1 (21–91)	<0.001
Female, <i>n</i> (%)	114 (87%)	92 (90%)	0.586
Body mass index	24.8 ± 5.1	24.1 ± 4.2	0.414
Bone density performed, <i>n</i> (%)	105 (80%)	90 (88%)	0.041
Bone density result, <i>n</i> (% of those with BMD)			<0.001 ^a
Osteoporosis (<i>t</i> -score ≤ −2.5)	29 (28%)	56 (62%)	
Low bone density (<i>t</i> -score ≤ −1.0 > −2.5)	32 (30%)	21 (23%)	
Normal bone density	40 (38%)	5 (6%)	
Fractures, <i>n</i> (% of total group)	45 (34%)	53 (52%)	0.010
Wrist	15 (11%)	13 (13%)	0.922
Arm	12 (9%)	4 (4%)	0.191
Shoulder	2 (2%)	5 (5%)	0.245
Ankle	2 (2%)	6 (6%)	0.143
Lower leg	5 (4%)	5 (5%)	0.715
Hip/femur	1 (0.8%)	6 (6%)	0.045
Pelvis	1 (0.8%)	2 (2%)	0.583
Vertebra	9 (7%)	13 (13%)	0.195
Rib	6 (5%)	9 (9%)	0.298
Respondents under age 50 years with history of fracture ^b	19 (35%)	11 (50%)	0.347

131 participants with CD and 102 participants without CD. Of those with CD, 87% were diagnosed in adulthood and 40% had no recognized gastrointestinal symptoms. In 21% CD was diagnosed after the diagnosis of osteoporosis and in 9% after a fracture.

Both CD and menopause lead to bone loss. Identifying CD in postmenopausal women should lead to modification of osteoporosis management.

Grazie per l'attenzione

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