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Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Seminario n°138: Enfermedades Inflamatorias Intestinales en el embarazo

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MAPA DE LA RUTA:

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ENFERMEDADES INFLAMATORIAS INTESTINALES (EII) EN EL EMBARAZO

- Introducción
- Diagnóstico
- Riesgos de EII en embarazo
- Riesgos de embarazo en EII
- Tratamiento y Seguimiento
- Vía de parto
- Lactancia y manejo RN
- Conclusiones

Introducción

- **Inadecuada activación del sistema inmune en la pared intestinal.**
- **Incluye a la enfermedad de Crohn (EC), Colitis Ulcerosa (CU) y enfermedades inflamatorias intestinales no especificadas.**
- **Incidencia EC: 5/100.000 peak 15-24 años.**
- **Incidencia CU 9,8/100.000 peak 25-34 años. La mitad antes de los 32 años**
- **El 25% se embaraza.**
- **La tasa de fertilidad en las mujeres con EII inactiva es similar a la de la población general, por el contrario, la EII activa se asocia a fertilidad disminuida.**

Diagnóstico

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- Colitis Ulcerosa: Inflamación intestinal que se inicia en el recto y continúa proximalmente hacia el colon, compromete hasta la membrana de la mucosa.

- Enfermedad de Crohn: Inflamación segmentaria del tubo digestivo, generalmente localizada en íleon terminal y colon proximal. Inflamación transmural.

R

Factores de riesgo

- Factores que modifican el debut y evolución de la enfermedad:
  - Uso de corticoides
  - Apendicectomía precoz reduce CU
  - Tabaquismo, protector para CU, aumenta el riesgo de EC
  - Edad
  - Antecedente de recaídas
  - Cirugía previa relacionada con EII
  - Tratamiento con anti-TNF/inmunosupresor

  - Embarazo: Factor independiente de evolución de enfermedad
  - La multiparidad disminuye el riesgo de requerir cirugía
  - Menor número de recaídas en multíparas (estudio observacional de 10 años)

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Riesgos de EII en Embarazo

- Riesgo de parto prematuro
  - CU activa OR 2,72
  - EC activa OR 2,66
- Riesgo de bajo peso al nacer:
  - CU activa OR 2,1
  - EC activa OR 3,3
- Mortinato OR 4,48

- **EII activa se asocia a:**
  - **Aborto**
  - **Mortinato**
  - **RNBP**
  - **Parto prematuro**
  - **Cesárea**

- El antecedente de cirugía intestinal es FR independiente para bajo peso y cesárea.
- DPPNI, corioamnionitis, RPM, PE, Eclampsia, distrés fetal, infecciones, transfusión materna, placenta previa, ITU por SGB más frecuentes.

Estado del arte en Enfermedad Inflamatoria Intestinal y embarazo. ACTECCU
Anna M. Maliszewska et al., Inflammatory bowel disease and pregnancy. Ginekologia Polska 2017, vol. 88, no. 7

Impacto del embarazo en las EII

- Embarazo con enfermedad activa:
  - EC: 1/3 permanece activa, 1/3 presenta exacerbación
  - CU: 50-70% permanece activa
- Embarazo con enfermedad en remisión: 70-80% se mantiene
  - EC: Exacerbaciones similar a no embarazada, 20%
  - CU: Aumentan 33%

- 2013 APT: ECCO EpiCom study:
  - EC: curso no varía mayormente
  - CU: mayor riesgo de recaída durante embarazo: RR 2,9
    - Post parto RR 6,2
    - Mayor probabilidad en 1er trimestre, disminuye a medida que progresa gestación.

Pedersen N. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. Aliment Pharmacol Ther. 2013 Sep;38(5): 501-12.

Tratamiento

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- En general se recomienda como objetivo principal llegar al embarazo en remisión y mantener esta condición durante la gestación.
- Mantener terapia pregestacional

- Contraindicados: Metotrexato y talidomida
- Casos aislados de RCIU, inmunodepresión fetal con Azatioprina y 6-mercaptopurina. (Clase D FDA)
- Ciclosporina (Clase C FDA) se ha asociado a RCIU y parto prematuro
- Biológicos anti TNF-alfa (inflixumab, adalimumab) resultados similares a población general

VERGARA A, María Teresa y REY G, Paula. Enfermedad inflamatoria intestinal y embarazo: experiencia de 16 años. Rev. méd. Chile [online]. 2011, vol.139, n.11, pp.1421-1427.

Tratamiento

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- 5-ASA (mesalazina)
- Antibióticos
- Tiopurinas
- Corticoides
- Biológicos (anti-TNF)

Ref

Mesalazinas

- Anti inflamatorio de la familia de los salicilatos
- El uso de sulfasalazina requiere la administración concomitante de ácido fólico 2mg
- Asacol contiene dibutilphtalato (DBP) que se asocia a malformaciones urogenitales, se recomienda cambiar de 5-ASA.

Table 1. Therapy during pregnancy

Drugs	Use in pregnancy	Influence on pregnancy
5-ASA		
Mesalamine	Category B Possible to apply Low risk	Does not increase the risk of stillbirth, congenital anomalies, preterm delivery, spontaneous abortion or low birth weight
Asacol (formulations containing dibutyl phthalate)	Category C Possible to apply Low risk	In animal studies, it causes urinary tract and skeletal system defects Recommended to change to mesalamine
Sulfsalazine	Category B Possible to apply Low risk	Crosses placental barrier Inhibits the absorption and metabolism of folic acid Supplementation up to 2 mg per day of folic acid is recommended during preconception period and pregnancy to prevent neural tube defects

Gaidos and Kane. Managing IBD Therapies in Pregnancy. Curr Treat Options Gastro (2017) 15:71–83

Antibióticos

- AMOXICILINA-CLAVULÁNICO: Bajo riesgo, de elección.

Antibiotics		
Metronidazole	Category B Do not use in the first trimester Low risk with short term use	Crosses placental barrier Single reports of teratogenicity, yet unconfirmed in studies both in humans and animals
Ciprofloxacin	Category C Do not use in the first trimester Low risk with short term use	Crosses the placenta In animal studies it affects bones and cartilage causing potentially arthritis Unconfirmed in human studies

Gaidos and Kane. Managing IBD Therapies in Pregnancy. Curr Treat Options Gastro (2017) 15:71–83

Tiopurinas

- Riesgo aumentado de malformaciones congénitas usando azatioprina y 6-mercaptopurina.
- Estudios más recientes no muestran diferencias en los resultados maternos o fetales usando tiopurinas, incluso en un estudio multicéntrico, se correlaciona con menos complicaciones neonatales.
- Seguimiento a 4 años de la descendencia demostró no haber trastornos del desarrollo ni alteraciones del sistema inmune.

Immunomodulators		
Thiopurines	Category D It is not recommended to start treatment during pregnancy because of side effects such as pancreatitis or leukopenia Low risk	Single reports of an increased incidence of preterm delivery and congenital ventricular and atrial septal defects
Cyclosporine	Category C Low risk	Crosses the placenta Possible toxic effects
Tacrolimus	Category C Low risk	Crosses the placenta May cause hyperkalemia and renal dysfunctions
Methotrexate	Category X Contraindicated Stop optimally 3 months before fertilization in men and 6 months in female	Crosses the placenta Teratogenic effects May lead to fetal death

Gaidos and Kane. Managing IBD Therapies in Pregnancy. Curr Treat Options Gastro (2017) 15:71–83

Corticoides

- El estudio prospectivo PIANO (Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes) no mostró riesgo aumentado de malos resultados neonatales, sin riesgo mayor de infecciones ni retraso del DSM o malformaciones congénitas.

- Presentó mayor riesgo de diabetes gestacional y bajo peso de nacimiento.

Corticosteroids		
Prednisolone	Category C Recommended low doses Low risk	Crosses the placenta Increased risk of SGA, gestational diabetes, early neonatal infection Single reports of increased incidence of cleft palate, ultimately unconfirmed
Budesonide	Category B/C Recommended low doses Low risk	Crosses the placenta High first-pass metabolism and less side effects

Gaidos and Kane. Managing IBD Therapies in Pregnancy. Curr Treat Options Gastro (2017) 15:71–83

Biológicos

- Infliximab y adalimumab los más usados. Cruzan la barrera placentaria, excepto Certolizumab.
- Niveles plasmáticos fetales y en cordón mayores que maternos tras uso en el tercer trimestre, detectables hasta 6-12 meses.

Anti-TNF agents They may cause decreased immunity, therefore live vaccines should be avoided during the first 6–12 months of life of the newborn exposed in utero		
Adalimumab	Category B Recommended to stop in third trimester Low risk	Crosses the placenta Does not increase the risk of birth defects, premature births, stillbirths, miscarriages or SGA
Certolizumab	Category B Can continue during pregnancy Low risk	Minimally crosses the placenta Does not increase the risk of premature labor or neonatal infection
Infliximab	Category B Recommended to stop in third trimester Low risk	Crosses the placenta Does not increase the risk of preterm delivery or neonatal infection
Golimumab	Category B Recommended to stop in third trimester Low risk	Crosses the placenta

Gaidos and Kane. Managing IBD Therapies in Pregnancy. Curr Treat Options Gastro (2017) 15:71–83

Otros tratamientos

- Terapia combinada inmunosupresor+anti-TNFa aumentan las infecciones en el lactantemenor. RR 1.50 (1.08–2.09)

Drugs	Use in pregnancy	Influence on pregnancy
Anti-integrins		
Natalizumab	Category C Limited human data Recommended to stop 3 months before pregnancy	Possible placental transfer Increases the risk of spontaneous abortion
Vedolizumab	Category B Limited human data	Possible placental transfer
Anti-IL-12/23 drugs		
Ustekinumab	Limited human data	

Surgery

Indications for surgery do not differ in the pregnant patient and include bowel obstruction, perforation, and medically refractory disease. Nonemergent surgery should preferentially be performed during the second trimester.[93] Maternal and fetal outcomes after colectomy for fulminant disease may be improving, in contrast to historic data showing high maternal and fetal morbidity and mortality.[94]

McConnell & Mahadevan. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin N Am 45 (2016) 285–301.

Manejo de la crisis

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Box 1
Managing inflammatory bowel disease exacerbations during pregnancy

Evaluation

- Rule out *Clostridium difficile* infection, which is more prevalent in the peripartum period.
- Interpret laboratory tests with caution: low albumin, low hemoglobin, and elevated erythrocyte sedimentation rate are common in pregnancy and may not reflect inflammation.
- Unsedated flexible sigmoidoscopy to assess disease severity can be performed safely in any trimester.
- Full colonoscopy is rarely necessary and requires anesthesia with fetal monitoring.
- MRI is preferred over computed tomography to avoid fetal radiation exposure. Gadolinium is a potential teratogen and should be avoided in the first trimester.

Treatment

- Use corticosteroids at the lowest effective dose and for the shortest necessary duration.
- Consider budesonide when clinically appropriate.
- Stress dosing may be necessary during labor and delivery to avoid adrenal insufficiency.
- Aminosalicylates, corticosteroids, and biologics may be used for induction therapy in pregnancy.
- If an antibiotic is needed, amoxicillin-clavulanic acid has a favorable safety profile.
- Nonemergent surgery should be performed in the second trimester.

McConnell & Mahadevan. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin N Am 45 (2016) 285–301.
Sally J Bell, Emma K Flanagan. Narrative review: Updates in the management of inflammatory bowel disease during pregnancy. MJA 2019.

Seguimiento

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Table 2
Checklist for managing the patient with inflammatory bowel disease before, during, and after pregnancy

Time Period	Task
Preconception	Establish care with multidisciplinary team: primary care physician, gastroenterologist, obstetrician, maternal-fetal medicine specialist Update health care maintenance, vaccinations, and surveillance colonoscopy as appropriate Check baseline laboratories (complete blood count, iron studies, B12, folate, vitamin D) and correct any nutrient deficiencies Assess disease activity • Consider baseline fecal calprotectin or colonoscopy if appropriate Optimize disease control • Adjust medications to achieve steroid-free remission • Discontinue methotrexate and switch to an alternate agent Develop medication plan for pregnancy and postpartum period • Communicate plan to all providers • Ensure patient understands and is in agreement
First trimester	Continue maintenance medications
Second trimester	Continue maintenance medications Consider therapeutic drug monitoring of biologics and dosing adjustments
Third trimester	Continue maintenance medications Consider adjusting biologic medication dosing schedule to reduce placental transfer Last dose: • Infliximab: week 30–32 • Adalimumab: week 36–38 • Certolizumab pegol: no adjustment • Golimumab: week 34–36 • Natalizumab: week 36 • Vedolizumab: week 30–32 Consider serial ultrasonographic assessment of fetal growth beginning at week 26–28, especially with active disease or inadequate maternal weight gain
Delivery	Mode of delivery determined by obstetric considerations • Active perianal disease is an indication for cesarean delivery
Postpartum	Resume biologic therapy if interval appropriate and no infection • 24 h after vaginal delivery • 48 h after cesarean delivery Review safety of continuing most medications during lactation Inform pediatrician of in utero biologic medication exposures Avoid live vaccines for at least 6 mo or until infant drug level becomes undetectable (applies to all biologic agents except certolizumab pegol)

McConnell & Mahadevan. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin N Am 45 (2016) 285–301.

Seguimiento

- Hemoglobina
- Albumina
- PCR
- Calprotectina fecal: permite monitorizar actividad de enfermedad
  - Mayor a 250ug/g se correlaciona con actividad

- Ecografía abdominal hasta las 32 semanas o RM sin gadolinio
- Endoscopía en caso de presentar "*flares*"

Sally J Bell, Emma K Flanagan. Narrative review: Updates in the management of inflammatory bowel disease during pregnancy. MJA 2019.

Vía de parto

- Según indicación obstétrica.
- Los casos de enfermedad activa que comprometa región perineal o recto deben interrumpirse vía cesárea.
- En casos de enfermedad en remisión, el parto no otorga mayor morbilidad ni riesgo de enfermedad perineal. Debe evitarse el uso de episiotomía, no obstante, es preferible al desgarro no controlado.
- Parto vaginal (PV) no se asoció a incontinencia fecal
- Colostomía o ileostomía no contraindican PV
- El antecedente de cirugía con anastomosis ileo-anal es indicación relativa de cesárea.

Anna M. Maliszewska et al., Inflammatory bowel disease and pregnancy. Ginekologia Polska 2017, vol. 88, no. 7

Lactancia y manejo RN

- 44,2-83,3% de las puérperas con EII dan lactancia
- Podría ser factor protector de recaída durante el primer año post parto.

Table 2. Therapy during lactation

Drugs	Influence on lactation	Additional impact
5-ASA Increases levels of free bilirubin, potentially leading to kernicterus		
Mesalamine	Low risk	Single cases of neonatal diarrhea
Asacol	Low risk	
Sulfsalazine	Low risk	
Antibiotics		
Metronidazole	Avoid prolonged course of treatment Breastfeeding after 12–24 h	Potential toxicity in the infant due to prolonged course of treatment
Ciprofloxacin	Avoid prolonged course of treatment Breastfeeding after 48 h	Prolonged course of treatment may result in neonatal arthropathies
Corticosteroids		
Prednisolone	Low risk Breastfeeding after 4 h	
Budesonide	Low risk	

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Lactancia y manejo RN

Immunomodulators		
Thiopurines	Low risk Breastfeeding after 4 h	
Cyclosporine	Contraindicated High concentration in breast milk	Potential immunosuppressive effect Toxicity
Tacrolimus	Low risk	Single reports on safety in use
Methotrexate	Contraindicated High concentration in breast milk	Toxicity
Anti-TNF drugs	Limited data	Low concentrations in breast milk and poor absorption lead to subtherapeutic concentrations in the neonate's blood
Adalimumab	Low risk	
Certolizumab	Low risk	Undetectable in breast milk
Infliximab	Low risk	
Golimumab	Limited data, low risk	
Anti-integrins		
Natalizumab	Limited data	
Vedolizumab	Limited data	
Anti-IL-12/23 drugs		
Ustekinumab	Limited data	

- Precaución de no vacunar con agentes vivos al RN los primeros 6 meses si se ha usado anti-TNF en la madre durante la gestación.

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Conclusiones

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- Manejo multidisciplinario de estas pacientes, manejo por obstetra, perinatólogo, gastroenterólogo, cirujano digestivo, nutricionista y nutriólogo.

- Importancia de educar a las pacientes respecto a la adherencia al tratamiento.

- Relevancia de la consulta preconcepcional para adecuar la terapia en caso de ser necesario, evitar embarazo en periodo de crisis.

1 In most women with inflammatory bowel disease (IBD), the condition is diagnosed during prime child-bearing years

With 1 in 150 Canadians affected and more than half of them female, Canada has among the highest incidence and prevalence rates of IBD in the world.[1]

2 Active IBD (Crohn disease or ulcerative colitis) during conception and pregnancy increases the risk of adverse pregnancy outcomes

Adverse outcomes include prematurity, intrauterine growth restriction, spontaneous abortion, stillbirth and neonatal death.[2] Therefore, preconception care and regular review of disease activity by a gastroenterologist during pregnancy are important.[3]

3 Except for methotrexate, IBD therapies should be continued throughout pregnancy and lactation to opti mize and maintain disease control[4]

Women taking methotrexate should stop using it at least three months before attempting to conceive.[4] Corticosteroids should be used with caution given the risk of gestational diabetes and hypertension.[4] 5-Aminosalicylic acid (5-ASA) compounds and azathioprine can be safely continued.[4] To minimize transplacental transfer, the last dose of biologic therapies in pregnancy, including anti–tumour necrosis factor-alpha (anti-TNF-α) therapy, should be provided in the middle of the third trimester and resumed immediately post partum.[4] Because there is minimal transmammary transfer of IBD therapies, breastfeeding is encouraged.[4]

4 Vaginal delivery should be considered in women with IBD unless they have active perianal disease or have undergone an ileoanal anastomosis[4]

Historically, population-based studies have shown that women with IBD are at higher risk of cesarean delivery than women in the general population in the absence of defined gastroenterologic or obstetric indications.[4]

5 Transplacental transfer of biologic therapies, specifically anti-TNF-α therapy, means that the live rotavirus vaccines scheduled at two and four months of age should be omitted[5]

All other live vaccines should be provided according to the Canadian Immunization Guide, including live measles–mumps–rubella and varicella vaccines at 12 months of age, because the anti-TNF-α drug will have cleared by then.[5] Expert advice should be sought if other live vaccines (e.g., yellow fever and bacille Calmette–Guérin vaccines) are required before 12 months of age for travel indications.

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Amelie I. Stritzke MD, Cynthia H. Seow MBBS(Hons). PRACTICE: FIVE THINGS TO KNOW ABOUT...Inflammatory bowel disease in pregnancy. CMAJ 2017 May 8;189:E669. doi: 10.1503/cmaj.160967

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