GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT:
Induction for Fetal Macrosomia Reduces the Risk of Shoulder Dystocia and Infant Fractures

- Allopurinol for Cirrhosis: New Use for an Old Drug?
- Best for Bones: PTH or Bisphosphonates?
- Sound Waves of the Heart: Evaluating Ejection Fraction Using POCUS
- To Treat or Not to Treat: The Case for Antibiotics in Idiopathic 2nd Trimester Vaginal Bleeding

Induction for Fetal Macrosomia Reduces the Risk of Shoulder Dystocia and Infant Fractures

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Induction of Labour at or Near Term for Suspected Fetal Macrosomia

Boulvain M, Thornton JG. Induction of labour at or near term for suspected fetal macrosomia. *Cochrane Database Syst Rev.* 2023;3(3):CD000938. Published 2023 Mar 8. doi:10.1002/14651858.CD000938.pub3

KEY TAKEAWAY: Induction at or near term for suspected fetal macrosomia can reduce the risk of shoulder dystocia, infant fractures, and birthweight, but does not reduce the risk of cesarean section, instrumental delivery, or low arterial cord blood gas pH.

STUDY DESIGN: Systematic review and meta-analysis of four randomized controlled trials (RCTs) (N= 1,190)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Fetal macrosomia increases risks to infant and mother at the time of delivery such as shoulder dystocia, infant fractures, instrumental deliveries, need for a cesarean section, perineal lacerations, low arterial cord gas pH, infant brachial plexus injuries. The American College of Obstetricians and Gynecologists currently recommends avoiding cesarean delivery to reduce the risk of potential birth trauma unless the estimated fetal weight is at least 5,000 g in women without diabetes or at least 4,500 g in women with diabetes. However, under that threshold, there are no recommendations specifically for early or term inductions to reduce risks associated with fetal macrosomia.

PATIENTS: Pregnant women

INTERVENTION: Induction labor

CONTROL: Expectant management

PRIMARY OUTCOME: Cesarean section, instrumental delivery, shoulder dystocia, infant fracture, brachial plexus injury, low arterial cord blood pH

Secondary Outcome: Spontaneous delivery, third- and fourth-degree anal sphincter tears, perinatal mortality, intraventricular hemorrhage, mean infant birthweight

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria were women who had a fetus with estimated fetal weight (EFW) between 4,000–4,750 g, EFW >95th percentile, and EFW >97th percentile depending on the RCT.
- Women with gestational diabetes were excluded except for one RCT. In that RCT, only women who were diet-controlled gestational diabetics were included.
  - Four randomized controlled trials were included and were conducted in Europe and the USA.
- The intervention was the induction of labor at early term or term (37+0 to 38+6 weeks gestational age) and within 72 hours after randomization.
  - The method of induction was not specified and was left up to the clinician.
  - One study proceeded with cesarean section for EFW >4,500 g.
- The control was expectant management which included an induction after 42 weeks gestational age if not delivered by that time.
- Primary and secondary outcomes were assessed with an intent-to-treat model and relative risks were determined for the following outcomes:
  - Primary outcomes: Cesarean section, instrumental delivery, shoulder dystocia, infant fracture, brachial plexus injury, low arterial cord blood pH
  - Secondary outcomes: Spontaneous delivery, third- and fourth-degree anal sphincter tears, perinatal mortality, intraventricular hemorrhage, mean infant birthweight

INTERVENTION (# IN THE GROUP): 590

COMPARISON (# IN THE GROUP): 600

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- Labor induction did not affect the following compared to expectant management:
  - Cesarean delivery (risk ratio [RR] 0.91; 95% CI, 0.76–1.1)
  - Instrumental delivery (RR 0.86; 95% CI, 0.65–1.1)
  - Brachial plexus injury (RR 0.21; 95% CI, 0.01–4.3)
  - Infant asphyxia (RR 1.5; 95% CI, 0.25–9.0)
  - Low arterial cord blood pH (RR 1.0; 95% CI, 0.46–2.2)

- Labor induction reduced the risk of shoulder dystocia compared to expectant management (RR 0.60; 95% CI, 0.37–0.98).
- Labor induction reduced the risk of any infant fracture compared to expectant management (RR 0.20; 95% CI, 0.05–0.79; NNT=60).

Secondary Outcome –

- Labor induction reduced mean infant birthweight (mean difference –178 g; 95% CI, –315 to –40; I^2=89%).
- Labor induction did not affect the rate of spontaneous vaginal deliveries, anal sphincter tears, intraventricular hemorrhage, or NICU admissions compared to expectant management.
- No perinatal mortality events were reported across all RCTs.

LIMITATIONS:

- Due to individual study design and heterogeneity, there may be a greater effect on the reduction of birthweight and other adverse outcomes if a standard time for induction was set.
- For the trials that implemented inductions near 37 to 38 weeks gestation, there was a larger, more consistent difference in birth weight.
- While a benefit was found, there was no difference in mortality or long-term outcomes measured that would likely support a change in practice as no deaths were reported.
- Third-trimester ultrasounds diagnose fetal macrosomia can be inaccurate and introduce iatrogenic harm by an unnecessary change in management, but this is the best current method to evaluate fetal weight.

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Allopurinol for Cirrhosis: New Use for an Old Drug?

Allopurinol Prevents Cirrhosis-Related Complications: A Quadruple Blind Placebo-Controlled Trial

Glal KAM, El-Haggar SM, Abdel-Salam SM, Mostafa TM. Allopurinol Prevents Cirrhosis-Related Complications: A Quadruple Blind Placebo-Controlled Trial. *Am J Med.* 2024;137(1):55-64. doi:10.1016/j.amjmed.2023.09.016

KEY TAKEAWAY: Allopurinol decreases the incidence of hepatic decompensation events by 56% in patients with cirrhosis predominantly caused by viral hepatitis.

STUDY DESIGN: Randomized, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with cirrhosis frequently experience decompensation events and chronic inflammation may be an underlying mechanism. Allopurinol has anti-inflammatory properties and has been shown to decrease inflammatory markers. This study evaluated the effect of allopurinol on the occurrence of decompensation events.

PATIENTS: Adults with cirrhosis

INTERVENTION: Allopurinol

CONTROL: Placebo

PRIMARY OUTCOME: Occurrence of any decompensation event

Secondary Outcome: Occurrence of individual decompensation event

METHODS (BRIEF DESCRIPTION):

- The researchers included adults 18–75 years old with cirrhosis currently compensated but with a history of at least one decompensation event, a Child-Pugh score of B or C, and a Model of End-Stage Liver Disease (MELD) score <25.
- Decompensation events included:
  - Ascites
  - Variceal bleeding
  - Hepatic encephalopathy
  - Hepatorenal syndrome
  - Spontaneous bacterial peritonitis
- Researchers excluded patients with active spontaneous bacterial peritonitis, creatinine >2.0 mg/dL, hemoglobin <8 g/dL, hypovolemia, or electrolyte abnormalities.
- Patients were randomized 1:1 to either:
  - Allopurinol 300 mg daily for 24 weeks
  - Matched placebo pill
- Patients, physicians, outcome assessors, and data collection personnel were blinded to treatment assignment.
- All patients continued their previous treatments for cirrhosis and were followed up by phone weekly and clinic visits monthly.
- The primary outcome was the occurrence of any decompensation event defined as:
  - Ascites as diagnosed by exam or ultrasound.
  - Spontaneous bacterial peritonitis defined as positive ascitic fluid culture or ascitic fluid polymorphonuclear leukocyte count of ≥250 cells/mm^3.
  - Jaundice as diagnosed clinically or by bilirubin >5 mg/dL.
  - Hepatic encephalopathy was noted by an increase in Conn score of one grade.
  - Variceal bleeding as confirmed by upper endoscopy.
  - Hepatorenal syndrome was defined as a 100% increase in creatinine over <2 weeks.

INTERVENTION (# IN THE GROUP): 50

COMPARISON (# IN THE GROUP): 50

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Allopurinol decreased decompensation events compared to placebo over six months (32% vs 72%, respectively; hazard ratio [HR] 0.44; 95% CI, 0.27–0.62; NNT=3).

Secondary Outcome –

- Of the individual decompensation events, the allopurinol group had significantly less of the following compared to placebo:
  - SBP (HR 0.25; 95% CI, 0.05–0.76)
  - Hepatorenal syndrome (HR 0.2; 95% CI, 0.04–0.87)
- Allopurinol and placebo had similar incidences of ascites, jaundice, hepatic encephalopathy, and variceal bleeding events.

LIMITATIONS:

- The 95% CI reported in the study for the secondary outcome of ascites appears to be a misprint. The study clearly reported this as a significant difference despite the 95% CI indicating otherwise.
- The etiology of cirrhosis was viral hepatitis in 96% of the patients in the study.
- Unknown if populations with greater incidence of alcohol liver disease would see similar results.
- The study was underpowered to detect differences in uncommon adverse events or mortality.

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Best for Bones: PTH or Bisphosphonates?

Randomized Controlled Trial of Daily Teriparatide, Weekly High-Dose Teriparatide, or Bisphosphonate in Patients with Postmenopausal Osteoporosis: The TERABIT Study

Chiba K, Okazaki N, Kurogi A, et al. Randomized controlled trial of daily teriparatide, weekly high-dose teriparatide, or bisphosphonate in patients with postmenopausal osteoporosis: The TERABIT study [published correction appears in Bone. 2022 Sep;162:116484. doi: 10.1016/j.bone.2022.116484]. *Bone*. 2022;160:116416. doi:10.1016/j.bone.2022.116416

KEY TAKEAWAY: Daily teriparatide parathyroid hormone (PTH), weekly PTH, and oral bisphosphonates increase cortical bone thickness. However, daily or weekly PTH does not increase bone thickness more than bisphosphonates.

STUDY DESIGN: Multicenter, open-label, randomized, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Teriparatide is used for severe osteoporosis but performance compared to bisphosphonates is currently unknown. The objective of this study was to investigate the effects of daily PTH and weekly PTH on measures of bone density compared to oral bisphosphonates in postmenopausal osteoporotic patients.

PATIENTS: Post-menopausal women with osteoporosis with history of fragility fractures

INTERVENTION: Daily or weekly teriparatide

CONTROL: Oral bisphosphonates

PRIMARY OUTCOME: Percent change in bone cortical thickness

Secondary Outcome: Change in imaging scores and other biochemical markers

METHODS (BRIEF DESCRIPTION):

- 131 postmenopausal osteoporotic women with a history of fragility fractures were recruited from 18 hospitals and clinics in Japan with an average age of 72 years old.
    - Inclusion criteria: Females 60–89 years old, with a history of a fragility fracture (vertebral body fracture, proximal femoral fracture, distal radius fracture, proximal humerus fracture, rib fracture, pelvic fracture, or lower leg fracture).
    - Exclusion criteria: Serious heart disease, serious liver disease, serious renal impairment, serious diabetes mellitus, endocrine disorder affecting bone turnover, rheumatoid arthritis, motor paralysis, history of steroid use, history of use of osteoporosis medications within the past six months, drug hypersensitivity, and contraindications to any of the drugs used.
- Study participants were randomly allocated to one of the three treatment groups (daily PTH, weekly PTH, or bisphosphonates).
    - Daily PTH (D-PTH): Teriparatide 20 microgram SQ
    - Weekly PTH (W-PTH): Teriparatide 56.5 microgram SQ
    - Control: Weekly oral bisphosphate (BP): Alendronate 35 mg or risedronate 17.5 mg
- All three groups took alfacaldicol 1 microgram PO daily (an activated formulation of vitamin D).
- The primary outcome measured was the rate of change in cortical bone thickness (Ct.Th) after 18 months.
- Secondary outcomes measured included the rate of change in dual-energy X-ray absorptiometry (DXA), bone turn-over markers (BTM), high-resolution peripheral quantitative CT (HR-pQCT), and bone microarchitecture (evaluated through trabecular bone, cortical bone, and estimated bone strength).
    - Secondary outcomes were measured at baseline, six months, and 18 months of treatment.
- In addition, participants' medication adherence was confirmed using a dedicated diary. Information was collected on all adverse events that occurred during the treatment period.

INTERVENTION (# IN THE GROUP): 65

COMPARISON (# IN THE GROUP): 38

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- D-PTH increased cortical bone thickness of the distal radius at 18 months compared to baseline (1.3% change; 95% CI, 0.1–2.3).
- W-PTH increased cortical bone thickness of the distal radius at 18 months compared to baseline (0.6% change; 95% CI, 0.2–2.4).
- Oral BP increased cortical bone thickness of the distal radius at 18 months compared to baseline (0.5% change; 95% CI, 0.0–1.4).
- There was no significant difference between the change in cortical bone thickness of the distal radius at 18 months between D-PTH, W-PTH, or oral BP when compared to each other (1.3% vs 0.6% vs 0.5% change, respectively; *P*>.05).
- D-PTH increased cortical bone thickness of the distal tibia at 18 months compared to baseline (3.9% change; 95% CI, 1.7–5.3).
- W-PTH increased cortical bone thickness of the distal radius at 18 months compared to baseline (3.6% change; 95% CI, 2.1–4.4).
- Oral BP increased cortical bone thickness of the distal radius at 18 months compared to baseline (3.4% change; 95% CI, 1.9–6.7).
- There was no significant difference between the change in cortical bone thickness of the distal tibia at 18 months between D-PTH, W-PTH, or oral BP when compared to each other (3.9% vs 3.6% vs 3.4% change, respectively; *P*>.05).

Secondary Outcome –

- D-PTH significantly increased lumbar spine density at 18 months compared to oral BP from baseline (12% vs 6.8% change, respectively; *P*<.05).
- D-PTH significantly decreased bone density of the distal third of the radius at 18 months compared to oral BP from baseline (–4.1% vs –1.4% change, respectively; *P*<.05).
- There was no significant difference between D-PTH and oral BP in total hip bone density at 18 months.
- W-PTH significantly increased lumbar spine density at 18 months compared to D-PTH and oral BPs from baseline (8.5% vs 12% vs 6.8% change, respectively; *P*<.05).
- W-PTH significantly decreased bone density of the distal third of the radius at 18 months compared to D-PTH and oral BP from baseline (–3.0% vs –4.1% vs –1.4%, respectively; *P*<.05).
- There was no significant difference between W-PTH and oral BP in total hip bone density at 18 months.
- On HR-pQCT, D-PTH significantly increased trabecular volumetric bone mineral density (Tb.vBMD) in the radius and tibia at six and 18 months compared to oral BP from baseline:
  - Radius distal 1/3 at six months (3.8% vs 0.6% change, respectively; *P*<.05)
  - Radius distal 1/3 at 18 months (6.4% vs 2.0% change, respectively; *P*<.05)
  - Tibia at six months (2.9% vs 0.8% change, respectively; *P*<.05)
  - Tibia at 18 months (3.7% vs 0.2% change, respectively; *P*<.05)
- At six and 18 months, D-PTH also significantly increased trabecular bone connectivity in the radius and tibia compared to oral BP from baseline:
  - Radius distal 1/3 at six months (–0.9% vs –0.5% change, respectively; *P*<.05)
  - Radius distal 1/3 at 18 months (–1.8% vs –0.6% change, respectively; *P*<.05)
  - Tibia at six months (7.7% vs 1.5% change, respectively; P<.05)
  - Tibia at 18 months (12% vs 2.1% change, respectively; P<.05)
- D-PTH significantly decreased cortical volumetric tissue mineral density (Ct.vTMD) at the radius at 18 months in comparison with W-PTH and oral BP from baseline (1.3% vs 0.6% vs 0.5% change, respectively; *P*<.05).

LIMITATIONS:

- High dropout rate in both the D-PTH group and the W-PTH group because of the following: Patients did not want to do self-injections, significant side effects, increased cost of medications, and patients had to pay out of pocket.
- Weekly PTH was not a standard treatment in Japan.
- The two types of bisphosphonates used in Japan were a lower dose compared to other countries.

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Sounds Waves of the Heart: Evaluating Ejection Fraction Using POCUS

E-Point Septal Seperation Accuracy for the Diagnosis of Mild and Severe Reduced Ejection Fraction in Emergency Department Patients

Núñez-Ramos JA, Pana-Toloza MC, Palacio-Held SC. E-Point Septal Separation Accuracy for the Diagnosis of Mild and Severe Reduced Ejection Fraction in Emergency Department Patients. *POCUS J*. 2022;7(1):160-165. Published 2022 Apr 21. doi:10.24908/pocus.v7i1.15220

KEY TAKEAWAY: Point-of-care ultrasound (POCUS) with E-point septal separation (EPSS) provides a reliable tool to diagnose reduced ejection fraction in emergency department (ED) patients with cardiovascular symptoms.

STUDY DESIGN: Single-site, retrospective, diagnostic cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Chest pain is a common symptom that can require extensive evaluation including a thoracic echocardiogram to establish left ventricular ejection fraction (LVEF). POCUS with EPSS has been studied previously to evaluate LVEF in dyspneic patients and perioperative elective patients. Still, there is scarce information about the accuracy of EPSS for diagnosing LVEF <50% in the emergency room setting. By evaluating the accuracy and setting appropriate parameters for POCUS EPSS, primary care physicians can quickly establish LVEF before a formal cardiology-interpreted thoracic echocardiogram.

PATIENTS: Adults with cardiovascular symptoms in the ED

INTERVENTION: POCUS EPSS

CONTROL: Transthoracic echocardiogram

PRIMARY OUTCOME: Diagnostic accuracy

METHODS (BRIEF DESCRIPTION):

- 96 patients from the ED at Hospital Universidad del Norte, Barranquilla, Colombia >18 years old with chest pain or dyspnea as a chief complaint from July 2019 to March 2021 were included in the study.
  - Exclusion criteria: Patients with shock, hypotensive, cardiac arrest at admission, who received inotropes and/or vasopressors.
- Demographics:
  - Median age 61 years old (range 52–76)
  - Male gender: 59/96
  - Hypertension diagnosis: 58/96
  - Type 2 diabetes mellitus diagnosis: 23/96
  - Heart Failure: 16/96
  - Acute coronary syndrome: 12/96
- One ED internist with formal POCUS training performed all POCUS EPSS exams before a formal transthoracic echocardiogram.
  - The physician had knowledge of the chief complaint and patient's clinical background including heart failure, hypertension, and acute coronary syndrome but was unaware of previous LVEF.
  - A transthoracic echocardiogram was performed by a cardiologist with a subspecialty in echocardiography.
  - LVEF was calculated with the Simpson Biplane formula.
  - The cardiologist was unaware of the POCUS evaluation result.
- Receiver operating characteristics (ROC) curves were obtained for the prediction of an ejection fraction of ≤40% and <50%.
- The best cut-off point was calculated with the Youden index (YI).
- The highest (YI) was obtained, and diagnostic accuracy was evaluated with sensitivity, specificity, and likelihood ratio (LR).

INTERVENTION (# IN THE GROUP): 96

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- EPSS can be an accurate tool to diagnose reduced LVEF <50% in ED patients with cardiovascular symptoms.
  - Area under the curve (AUC) ROC (0.9; 95% CI, 0.84–0.97) with the best cutoff at 9.5 mm:
    - Sensitivity: 0.80
    - Specificity: 0.92
    - Positive LR: 9.8
    - Negative LR: 0.22
- EPSS can be an accurate tool to diagnose reduced LVEF ≤40%.

- AUC ROC (0.91; 95% CI, 0.85–0.97) with the best cutoff at 9.5 mm:
  - Sensitivity: 0.91
  - Specificity: 0.81
  - Positive LR: 4.7
  - Negative LR: 0.11

LIMITATIONS:

- Small sample size
- One ED Internist performing the POCUS EPSS exam.
- The patient population sample was only an age range of 52–76 years old.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

To Treat or Not to Treat: The Case for Antibiotics in Idiopathic 2nd Trimester Vaginal Bleeding

Antibiotic Treatment Reduces the Intensity of Intraamniotic Inflammation in Pregnancies with Idiopathic Vaginal Bleeding in the Second Trimester of Pregnancy

Musilova I, Stranik J, Jacobsson B, Kacerovsky M. Antibiotic treatment reduces the intensity of intraamniotic inflammation in pregnancies with idiopathic vaginal bleeding in the second trimester of pregnancy. *Am J Obstet Gynecol.* 2024;230(2):245.e1-245.e14. doi:10.1016/j.ajog.2023.07.041

KEY TAKEAWAY: Antibiotics may decrease amniotic inflammation and microbial load in patients with idiopathic vaginal bleeding between 15.0–27.6 weeks gestational age.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to small sample size and results compared to baseline)

BRIEF BACKGROUND INFORMATION: Though idiopathic 2nd trimester bleeding is rare, no specific treatment guidelines are available. The use of antibiotics to decrease microbial burden and inflammation has not been formally explored. This study assessed if antibiotic administration can decrease both the inflammatory response and microorganism load after 2nd trimester bleeding.

PATIENTS: 2nd trimester pregnancies with idiopathic bleeding

INTERVENTION: Use of antibiotics

CONTROL: No antibiotic use

PRIMARY OUTCOME: Intraamniotic inflammation and microbial load

METHODS (BRIEF DESCRIPTION):

- Pregnant patients admitted with active 2nd trimester bleeding between January 2020 and February 2023.
- Inclusion criteria:
  - Adults with singleton pregnancy with gestational age (GA) 15+0 to 27+6 weeks
  - Bleeding determined to be from the uterus
  - Consent for amniocentesis at admission
- Exclusion criteria:
  - Fetus with structural or chromosomal abnormalities
  - Noted placenta previa, trauma as a source of bleeding, identified leakage of amniotic fluid, and regular uterine activity.
- Selected patients underwent amniocentesis to assess for inflammation and the presence of microorganisms via microbial invasion of the amniotic cavity (MIAC).
  - Microorganisms included *Ureaplasma spp*, *Mycoplasma hominis*, and *Chlamydia trachomatis*
- The treatment group defined as having initial interleukin-6 (IL6) levels >3000 pg/mL was started on three antibiotics.
- Drug regimen included:
  - Ceftriaxone 2 g every 24 hours up to four weeks
  - Clarithromycin 500 mg every 12 hours up to eight weeks
  - Metronidazole 500 mg every eight hours up to four weeks
- The control group was not given antibiotics and was followed expectantly.
- The outcome was measured by performing a repeat amniocentesis on the intervention group to assess for inflammation using levels of IL6 and the presence of microorganisms after the treatment period.

INTERVENTION (# IN THE GROUP): 25

COMPARISON (# IN THE GROUP): The same 25 patients

FOLLOW-UP PERIOD: Seven days

RESULTS:

Primary Outcome –

- Treatment with antibiotics decreased IL6 levels and microorganism load with repeat amniocentesis compared to initial lab values in patients with intraamniotic inflammation (median 3,457 vs 19,812 pg/mL; *P*=.0001).
- Amniotic fluid samples containing Ureaplasma species DNA had a lower microbial load at the time of follow-up amniocentesis compared to initial amniocentesis (median $1.5x10^5$ vs $8.0x10^7$ copies DNA/mL; *P*=.02).

LIMITATIONS:

- Subsequent amniocentesis was not performed in all patients.

- The treatment or intervention group was compared against itself, not the control group.
- The sample size was small.
- Only one amniotic fluid protein (IL6) was assessed.
- Unable to assess the antibiotic effect on perinatal outcomes.
- Possible confounding effects from corticosteroid administration.

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