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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Race Correction in Clinical Calculations — Is It Time to Reconsider?

By Mitchell Linder, MD

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Dr. Linder reports no financial relationships relevant to this field of study.

SYNOPSIS: Many clinical calculators use race as a predictive variable to assess risk for outcomes. Although most of the tools assume a genetic disposition for these outcomes, other factors, such as health disparities and other potential confounders, are more likely to be the underlying reasons for any race-related differences in outcomes.

SOURCE: Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight – reconsidering the use of race correction in clinical algorithms. *N Engl J Med* 2020;383:874-882.

This is a theoretical analysis evaluating multiple existing diagnostic algorithms and clinical prediction guidelines and their use of race or ethnicity categories as inputs for calculation. The authors identified 13 prominent tests and calculators in wide use today that each use race/ethnicity as a component in their formulas. Studies they identified include pulmonary function testing, the Fracture Risk Assessment tool (FRAX), the Simplified Calculated Osteoporosis Risk Estimation (SCORE), the Breast Cancer Surveillance Consortium Risk Calculator, the National Cancer Institute Breast Cancer Risk Assessment Tool, the Rectal Cancer Survival Calculator, the pediatric urinary tract infection calculator (UTICalc), the STONE score (used for prediction of possible kidney stones), the Vaginal Birth After Cesarean (VBAC) risk calculator, the Kidney Donor Risk Index, the estimated glomerular filtration rate (eGFR) calculator, The Society of Thoracic Surgeons Short-Term Risk Calculator, and The American Heart Association's Get with the Guidelines — Heart Failure.

They noted that this list is not all-inclusive but includes readily available examples about how

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pervasive the use of race/ethnicity is in medical decision-making tools.

The authors examined each of these by specialty to show how each equation uses "race-correction" and how each of these race adjustments potentially could negatively affect Black patients. In cardiology, the heart failure score predicts lower risks for Black patients (without having any rationale provided), and the authors noted this could cause clinicians and hospitals to devote less resources to these patients, since they are deemed lower risk. For nephrology, they specifically pointed out how calculators overestimate kidney function based on assumptions about race-related differences in creatinine and overestimate the potential for kidney transplant failure involving kidneys from Black donors. The STONE score also is noted to assign lower scores to Black patients, thereby potentially guiding clinicians away from a possible diagnosis. The VBAC calculator is noted to predict a lower chance of success for African American and Hispanic patients. This decreased predicted success rate is hypothesized to discourage these patients from an attempt at a trial of labor and, thus, further increase the disproportionately high rate of cesarean delivery that minorities experience already.

The authors urged a thorough review of existing tools by institutions, medical societies, and individual clinicians. They noted that to do this properly involves working to re-evaluate how clinicians conceptualize race and apply it to the care they provide.

■ COMMENTARY

Systemic racism abounds in the medical field, with clinical calculators as just one example where it can be seen. Past research has shown that commonly employed commercial prediction algorithms used to allocate healthcare also have underlying racial bias in how their calculations are made.[1] Unfortunately, we are not able to look under the hood to see the inner workings of the tools we often use. How, then, are clinicians to go about making evidence-based clinical decisions that incorporate guideline-supported rationale? The authors provided three novel criteria that clinicians should consider: "When developing or applying clinical algorithms, physicians should ask three questions: 1) Is the need for race correction based on robust evidence and statistical analyses (e.g., with consideration of internal and external validity, potential confounders, and bias)?; 2) Is there a plausible causal mechanism for the racial difference that justifies the race correction?; and 3) Would implementing this race correction relieve or exacerbate health inequities?"

Use of these types of questions could be helpful in identifying inherent bias and systemic racism that potentially may be harming our patients because of the automatic assumption that clinical assessment tools are de facto free of prejudice. It is the responsibility of each and every practitioner to provide unbiased and appropriate care for our patients. Making sure our clinical tools are based on these same principles is a good start. For example, as of June 1, 2020, the University of Washington labs have transitioned from using the eGFR formula to using one that excludes race as a variable.[2-4]

The inclusion of the VBAC calculator on this list is especially concerning for clinicians who use this score as their primary determinant for providing delivery option guidance to their patients. Analysis of this calculator specifically has shown that most of the race-related statistics that underpin the algorithm likely are related to social advantage or disadvantage, as opposed to being the result of any specific race.[5] Given these known assumptions that are built into the VBAC calculator, use of the tool becomes more dangerous, since it could serve to perpetuate health disparities by having potentially viable trial of labor after cesarean candidates steered to repeat cesarean delivery solely because of their race.

With the higher rate of maternal morbidity and mortality that minorities sustain in the United States and the world, it is our duty to look at the tools we use, such as the VBAC calculator, to determine what potential conflicts or biases are included and whether that opinion is valid and applicable to our patients.[6] Of course, that one step will not reverse entrenched

biases everywhere nor eliminate systemic racism in one sweep, but every act to combat inequalities is a worthwhile one to undertake. ■

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ABSTRACT & COMMENTARY

Tamoxifen for the Management of Bleeding Irregularities in Contraceptive Implant Users

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Dr. Rivlin reports no financial relationships relevant to this field of study.

SYNOPSIS: In this double-blind, randomized controlled trial, etonogestrel implant users with prolonged or frequent menses who took 10 mg of tamoxifen twice daily for seven days as needed for irregular bleeding had an average of 9.8 (95% confidence interval, 4.6-15.0) more consecutive days of amenorrhea over a 90-day period compared to those who took a placebo.

SOURCE: Edelman AB, Kaneshiro B, Simmons KB, et al. Treatment of unfavorable bleeding patterns in contraceptive implant users: A randomized controlled trial. *Obstet Gynecol* 2020;136:323-332.

The etonogestrel-containing implant is a highly effective method of contraception that has been associated with unpredictable bleeding patterns, including amenorrhea and infrequent, frequent, and/or prolonged bleeding.[1] Some implant users find these bleeding patterns unacceptable, which can lead to discontinuation of the contraceptive method.[2] Breakthrough bleeding from this progestin-only implant likely results from abnormal blood vessel development in the endometrium in the absence of estrogen. Currently, options for management of bleeding irregularities are limited. Tamoxifen, a selective estrogen receptor modulator, may inhibit endometrial angiogenesis, and therefore could provide a sustained effect after treatment completion.

This double-blind, randomized, placebo-controlled trial enrolled 112 implant users (ages 15 to 45 years) experiencing frequent bleeding (two or more independent bleeding episodes in 30 days) or prolonged bleeding (seven or more consecutive days of bleeding in 30 days). Exclusion criteria included having any of the following: other etiologies of irregular bleeding patterns (e.g., breastfeeding, postpartum, bleeding dyscrasias); a contraindication to tamoxifen use (e.g., history of a venous thromboembolism); or a three-year implant that would expire during the study time period.

Participants were randomized to take either 10 mg of tamoxifen twice daily for seven days after experiencing three consecutive days of bleeding, or an identical placebo. Participants then repeated these treatments as needed over a 90-day period with a maximum of three treatments, and recorded daily bleeding patterns by text message. Research staff and participants were blinded to treatment assignments. In the second half of the study, all participants entered a 90-day open-label phase in which both study arms received tamoxifen as needed.

Research subjects, recruited from Portland, OR, and Honolulu, were predominantly white with an average body mass index of 27. Both study arms were demographically similar. The tamoxifen group reported 9.8 more consecutive days of amenorrhea after the first treatment than the placebo group in the first 90 days (95% confidence interval [CI], 4.6-15.0; no *P* value provided). The placebo group experienced a similar benefit after the first tamoxifen treatment in the open-label phase.

At the end of the first 90 days of the study, median bleeding satisfaction (range, 0-100 mm) was higher in the tamoxifen group (62 mm) than in the placebo group (46 mm, $P = 0.023$). However, median implant satisfaction (range, 0-100 mm) was similar

for both groups at the end of both the 90-day time period (83 mm vs. 80.5 mm, $P = 0.369$) and at the end of the 180-day time period (81 mm vs. 81.57 mm, $P = 0.767$). Although few adverse events occurred in the study, participants taking tamoxifen were more likely to report fluid retention, headache, and mood changes.

■ COMMENTARY

As the use of long-acting, reversible methods of contraception increases, clinicians more commonly encounter etonogestrel implant users experiencing irregular bleeding patterns.[3] Although such bleeding is unlikely to cause harm, it can be irritating to patients, and is a commonly cited reason for method discontinuation.[4] Unfortunately, few options exist to manage this bleeding in a sustained way. Combined hormonal oral contraceptives can improve bleeding irregularities during therapy, but they provide no long-lasting effect after pill discontinuation.[5]

[Although tamoxifen improved bleeding patterns for many implant users, for some it made no difference.]

Edelman and colleagues showed a more sustained effect of tamoxifen after treatment discontinuation — with 9.8 more days of amenorrhea among tamoxifen users compared to placebo. Notably, the authors powered their study to find a 15-day difference between the two groups — which, ultimately, they did not find. They achieved statistical significance because of a higher participant retention rate than anticipated, since a higher sample size increases the power of a study.

However, statistical significance does not always indicate clinical significance. Do nine additional days of amenorrhea over a three-month time period make a difference to patients? Patient satisfaction may be a more important clinical indicator than amenorrhea days. The tamoxifen group had higher bleeding satisfaction over the first 90 days of the study compared to the placebo group, but implant satisfaction was the same between the two groups at both 90 days and at the end of the study.

In addition, one should consider the implications of taking tamoxifen to manage bleeding irregularities. Although few adverse events occurred in the study, any side effects may be more bothersome to a patient than irregular bleeding, depending on that patient's preferences. The authors describe challenges in study recruitment among both patients and clinicians because of concerns about taking a "cancer drug" to manage implant bleeding. Only implant users willing to take tamoxifen enrolled in the study, which introduces selection bias into a study population with already limited demographic generalizability.

The acceptability of tamoxifen to manage bleeding irregularities to a broader patient population is unclear. Presumably, many users choose the implant precisely because of its nondaily dosing. A question left unanswered by this study is just how acceptable do patients find periodically taking any medication to manage irregular bleeding.

As the authors note, although tamoxifen improved bleeding patterns for many implant users, for some it made no difference. Irregular bleeding patterns among progestin-only contraceptive users are multifactorial, resulting from more than just angiogenesis. Inflammatory and coagulation components likely also play a role and will not be affected by tamoxifen. Therefore, finding a one-size-fits-all treatment is challenging.

Overall, this study adds to an evolving toolbox of management options for irregular bleeding with the etonogestrel implant but does not solve the problem. The authors note that tamoxifen provides a treatment but not a cure. As with all contraceptive counseling and management, patient-centered care is key. In practice, one should avoid automatically recommending tamoxifen to all implant users experiencing bothersome bleeding patterns. Rather, a clinician should explore patient concerns and preferences using shared decision-making. The patient and clinician ultimately could decide on a course of tamoxifen if the patient should express interest and find the dosing, cost, potential side effects, and unpredictable outcomes acceptable. ■

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ABSTRACT & COMMENTARY

Outcomes in Pregnant Women Treated with Anti-Tumor Necrosis Factor-Alpha Biologic Therapy

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Dr. Eke reports no financial relationships relevant to this study.

SYNOPSIS: In this population-based cohort study of 1,027 infants born to women treated with anti-TNF-α biologic therapy, there was an increased prevalence of preterm birth (adjusted odds ratio [aOR], 1.61; 95% confidence interval [CI], 1.29-2.02), cesarean delivery (aOR, 1.57; 95% CI, 1.35-1.82), and small for gestational age neonates (aOR, 1.36; 95% CI, 0.96-1.92) when treatment with anti-TNF was compared to non-biologic systemic treatment. Since disease processes varied greatly in these pregnant women, it was difficult to rule out confounding by disease severity (confounding by indication).

SOURCE: Bröms G, Kieler H, Ekbom A, et al. Anti-TNF treatment during pregnancy and birth outcomes: A population-based study from Denmark, Finland, and Sweden. *Pharmacoepidemiol Drug Saf* 2020;29:316-327.

Anti-tumor necrosis factor-alpha (anti-TNF-α), biologic therapy (adalimumab, certolizumab-pegol, golimumab, etanercept, and infliximab) is increasingly being used in managing inflammatory arthritides (ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis) and Crohn's disease during pregnancy.[1,2] These inflammatory arthritides are known to be associated with adverse pregnancy outcomes.[3] In this population-based study in Denmark, Finland, and Sweden, Bröms and colleagues described their findings in pregnant women treated with anti-TNF-α biologic therapy compared to those treated with non-biologic systemic therapy (anti-malarials, azathioprine, corticosteroids, methotrexate, and sulfasalazine).[1] Women were eligible if they gave birth to a singleton infant between January 2006 and December 2013 in Denmark; January 2006 and December 2012 in Finland; and July 2006 and December 2013 in Sweden; and had their medical records completed in the national medical birth registers of these three countries.[1] Outcomes assessed included preterm birth at less than 37 weeks of gestation, small for gestational age (moderate and severe), and cesarean delivery (planned and emergent). For statistical analyses, descriptive statistics was performed to describe the study sample. Univariate logistic regression analyses then were done to estimate the probability of preterm birth, cesarean delivery, and small for gestational age for participants on an anti-TNF-α biologic therapy vs. a non-biologic systemic regimen. To control for confounding, the authors used multivariable logistic regression to define the models that best predicted the probability of outcomes (preterm birth, cesarean delivery, and small for gestational age) as a function of covariates (country, maternal age, parity, smoking, body mass index, previous surgeries, and maternal disease). Sensitivity analyses were done to identify pertinent associations between inflammatory arthritides/Crohn's disease observations, anti-TNF-α biologic therapy, model inputs, and predictions, leading to the development of better models.

Among 1,633,909 live births included in this population-based cohort study, 1,027 pregnant women were managed with anti-TNF biologic therapy, while 9,393 pregnant women were treated with non-biologic systemic treatment during the course of pregnancy. Rheumatoid arthritis was the most common indication for anti-TNF-α biologic therapy (52.3%), followed by Crohn's disease (23.1%). The most common anti-TNF-α biologic therapies used were etanercept (49.7%), adalimumab (25.0%), and infliximab (20.3%).

Anti-TNF-α biologic therapy increased the prevalence of preterm birth (adjusted odds ratio [aOR], 1.61; 95% confidence interval [CI], 1.29-2.02), cesarean delivery (aOR, 1.57; 95% CI, 1.35-1.82), and small for gestational age neonates (aOR, 1.36; 95% CI, 0.96-1.92) when treatment with anti-TNF-α biologic therapy was compared to non-biologic systemic treatment. The risk of preterm birth was somewhat reduced in Danish and Swedish women after controlling for previous surgery and hospitalization in multivariable analysis (aOR, 1.41; 95% CI, 1.10-1.80). However, sensitivity analyses had minimal effect on the results. Since disease processes varied greatly in these pregnant women, it was difficult to rule out confounding by disease severity (confounding by indication).

■ COMMENTARY

Anti-TNF-α biologic therapy works by blocking the actions of TNF-α and neutralizing its biologic effects.[4] TNF-α is an important pro-inflammatory and immunomodulatory cytokine, and it is critical for differentiation of dentritic cells, B-cells, and T-cells during pregnancy.[5] The levels of TNF-α increase throughout gestation, especially in women with Crohn's disease and inflammatory arthritides. Because of the unique structure of TNF-α inhibitors (monoclonal antibodies composed of human immunoglobulin G), trans-placental passage of these immunoglobulins increases as pregnancy progresses, primarily during the second half of pregnancy.[6] Since these drugs cross the placenta, they are assumed, theoretically, to affect the mother and the developing fetus. However, with limited data on the safety of anti-TNF-α therapy use during pregnancy, no harmful embryotoxic effects have been reported with use of anti-TNF-α therapy.[6]

[When used during pregnancy, it is advised to discontinue anti-TNF-α therapies approximately four to six weeks prior to delivery to allow time for fetal recovery from any immunosuppression.]

Trans-placental passage of anti-TNF-α therapy occurs by passive diffusion via binding to Fc receptors in placental syncytiotrophoblasts, and the rate of placental transfer can be influenced by molecular weight, lipid solubility, degree of ionization, and half-life.[6] The half-lives of adalimumab, certolizumab-pegol, and etanercept are 10 to 20 days, 11 to 14 days, and four to six days, respectively, while those for golimumab and infliximab are 10 to 18 days, and 7.7 to 9.5 days, respectively. This means it would take approximately four to six weeks for these drugs to be eliminated completely from the body after the last dose.

Since these medications have long half-lives, the major issue with their use in pregnant women and neonates is preterm birth and immunosuppression (and potentially increased risk for infection), respectively, although these have not been confirmed in prospective cohort studies. Anti-TNF-α therapy also is known to be secreted in breast milk.

As described by Bröms and colleagues, anti-TNF-α biologic therapy, when used in women with inflammatory arthritides and Crohn's disease, was associated with adverse pregnancy outcomes (preterm birth, small for gestational age, and cesarean deliveries). However, it is difficult to tease out if these adverse outcomes were the result of disease severity or the anti-TNF-α biologic therapy, or both. This special kind of confounding is known as confounding by indication. Confounding by indication is said to have occurred when a disease — the indication for drug use (or exposure) — independently affects the outcome.[7] Confounding by indication constitutes a major challenge in observational studies, and is one of the most difficult types of confounding to control. Although there are several studies that have used multivariable regression models to control for confounding by indication, propensity score-based analysis remains one of the best techniques to control for confounding by indication, since it provides a more precise estimate of treatment effect where confounding by indication is presumed to be present.

In conclusion, it is unclear how the findings of this study by Bröms and colleagues would translate to clinical practice, since confounding by indication was not adequately controlled for using appropriate statistical methods. When used during pregnancy, it is advised to discontinue anti-TNF-α therapies approximately four to six weeks prior to delivery to allow time for fetal recovery from any immunosuppression.

Anti-TNF-α biologic therapy can theoretically interfere with an infant's response to live vaccines, and, therefore, such vaccines should be avoided in these circumstances. In addition, anti-TNF-α therapies may increase the risk of systemic maternal and neonatal infections, reactivation of chronic diseases (such as tuberculosis), and development of lymphomas when used in pregnant women. ■

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ABSTRACT & COMMENTARY

Application of Acetic Acid to Identify Lesions During Colposcopy

By Rebecca H. Allen, MD, MPH, Editor

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SYNOPSIS: In this prospective study, one minute of acetic acid application was found to be sufficient to identify the most severe colposcopic lesion in 96.7% of subjects.

SOURCE: Hilal Z, Tempfer CB, Burgard L, et al. How long is too long? Application of acetic acid during colposcopy: A prospective study. *Am J Obstet Gynecol* 2020;223:101.e1-101.e8.

The appropriate duration of dilute acetic acid application to identify cervical dysplastic lesions during colposcopy examination is unknown. The authors of this study sought to determine the optimal length of time by video recording the colposcopy and identifying the most severe colposcopic lesion one, three, and five minutes after application.

From September 2018 to May 2019, a total of 300 women were recruited and underwent videocolposcopy for abnormal Pap smear results at two sites in Germany. Dilute acetic acid (5%) was applied to the cervix via a spray can. The colposcopist classified the most severe colposcopic lesion one, three, and five minutes after application. Investigators also documented the time to first appearance of and fading of the most severe colposcopic lesion. A total of 85 videos were randomly selected for a more detailed assessment, with a 1:2:2 ratio (negative for dysplasia:low-grade squamous intra-epithelial lesion [LSIL]:high-grade squamous intra-epithelial lesion [HSIL]) by three blinded colposcopists.

The average age of the participants was 35.2 years. Ninety-eight (37.8%) were smokers. The reason for referral to colposcopy included persistent human papilloma virus in 32 (10.7%), atypical squamous cells of undetermined significance in 11 (3.8%), atypical squamous cells in which HSIL could not be ruled out in 21 (7%), atypical glandular cells in 12 (4.0%), LSIL in 69 (23%), HSIL in 146 (48.6%), adenocarcinoma in-situ in eight (2.7%), and squamous cell carcinoma in one (0.3%). At the end of the colposcopy, five minutes after application of acetic acid, colposcopic assessment found a normal cervix in 61 (23.1%), minor changes in 107 (40.5%), and major changes in 92 (34.9%) cases. After one minute, 290 of 300 subjects (96.7%) were diagnosed with the most severe colposcopic lesion. This did not improve after three or five minutes. The median time from application of acetic acid to the first appearance of the most severe colposcopic lesion was found to be 13.5 seconds (interquartile range [IQR], three to 27.25 seconds), which was significantly lower for HSIL compared to LSIL lesions ($P < 0.001$). The fading of acetowhite lesions occurred over time, with the median time from application to the start of fading at 191 seconds (IQR, 120 to 295 seconds). Fading started earlier in HSIL compared to LSIL lesions ($P = 0.044$).

■ COMMENTARY

The authors of this study evaluated the optimal duration of acetic acid application to identify colposcopic lesions. Studies that evaluate our current clinical practice are highly interesting. Many times, clinicians practice a certain way because of how they were trained, and the evidence behind these practices often is not examined. Colposcopy practice in the United States is governed by the American Society for Colposcopy and Cervical Pathology (ASCCP). Colposcopy is a technique for the evaluation of cervical and vaginal lesions under magnification to allow for directed biopsies. In 2017, the organization published recommendations for colposcopy practice in the United States, which had been lacking previously.[1]

These guidelines addressed recommendations for colposcopy practice, including standardizing terminology, reporting, and colposcopy procedures, including the number and types of biopsies. They determined the minimum criteria for reporting should include the following: squamocolumnar junction visibility (fully/not fully), acetowhitening (yes/no), lesion(s) present (acetowhite or other, yes/no), and colposcopic impression (normal/benign, low-grade, high-grade, cancer). They also recommended that, in general, multiple biopsies targeting all areas with acetowhitening, metaplasia, or higher abnormalities are recommended. Usually, at least two, and up to four, targeted biopsies from distinct acetowhite lesions should be taken.[1] Furthermore, the guidelines recommend

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examining the cervix with magnification after application of 3% to 5% acetic acid.[2] However, the ASCCP guidelines do not mention how long to wait after the application of the acetic acid.

The authors of this study found that 97% of participants were diagnosed with the most severe colposcopic lesion one minute after acetic acid application. This is important information for colposcopy practice, since the provider should not evaluate the lesion too early or it might be missed, nor too late, since it might fade, as was documented in 78% of cases in this study. It was also noted that HSIL stains very quickly, within seven seconds, but also fades earlier than LSIL. This fading phenomenon has been documented previously, which is why many colposcopists repeat acetic acid application throughout the procedure. I found this study fascinating because I do not remember ever being trained in the optimal duration of acetic acid application. Knowing the majority of lesions will appear after one minute of acetic acid application may help us to not prolong the procedure for the patient. ■

REFERENCES

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CME/CE QUESTIONS

1. **Using race as a data point in clinical algorithms:**
   a. leads to better outcomes for all patients.
   b. should be looked upon warily, since most often there are underlying causes that contributed to the outcomes used in the creation of the algorithms, not patient race itself.
   c. is always important.
   d. is appropriate if the data used to create the algorithm showed race as a contributing factor to the outcome.
2. **In the study by Edelman et al, patients with irregular bleeding patterns associated with an etonogestrel contraceptive implant who took tamoxifen experienced which of the following bleeding patterns when compared to those who took placebo?**
   a. 9.8 more consecutive days of amenorrhea over a 90-day time period
   b. 23.1 more consecutive days of amenorrhea over a 90-day time period
   c. 9.8 more days of spotting over a 90-day time period
   d. 23.1 more days of spotting over a 90-day time period
3. **Which of the following medications is *not* an anti-tumor necrosis factor-alpha therapy used in the management of inflammatory arthritides during pregnancy?**
   a. Golimumab
   b. Natalizumab
   c. Infliximab
   d. Certolizumab-pegol
4. **In the study by Hilal et al, the best time to identify colposcopic lesions after acetic acid application was found to be:**
   a. 30 seconds.
   b. one minute.
   c. three minutes.
   d. five minutes.

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