

False Positive Serum Pregnancy Testing in Patients with Elevated Autoimmune Antibodies

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Introduction

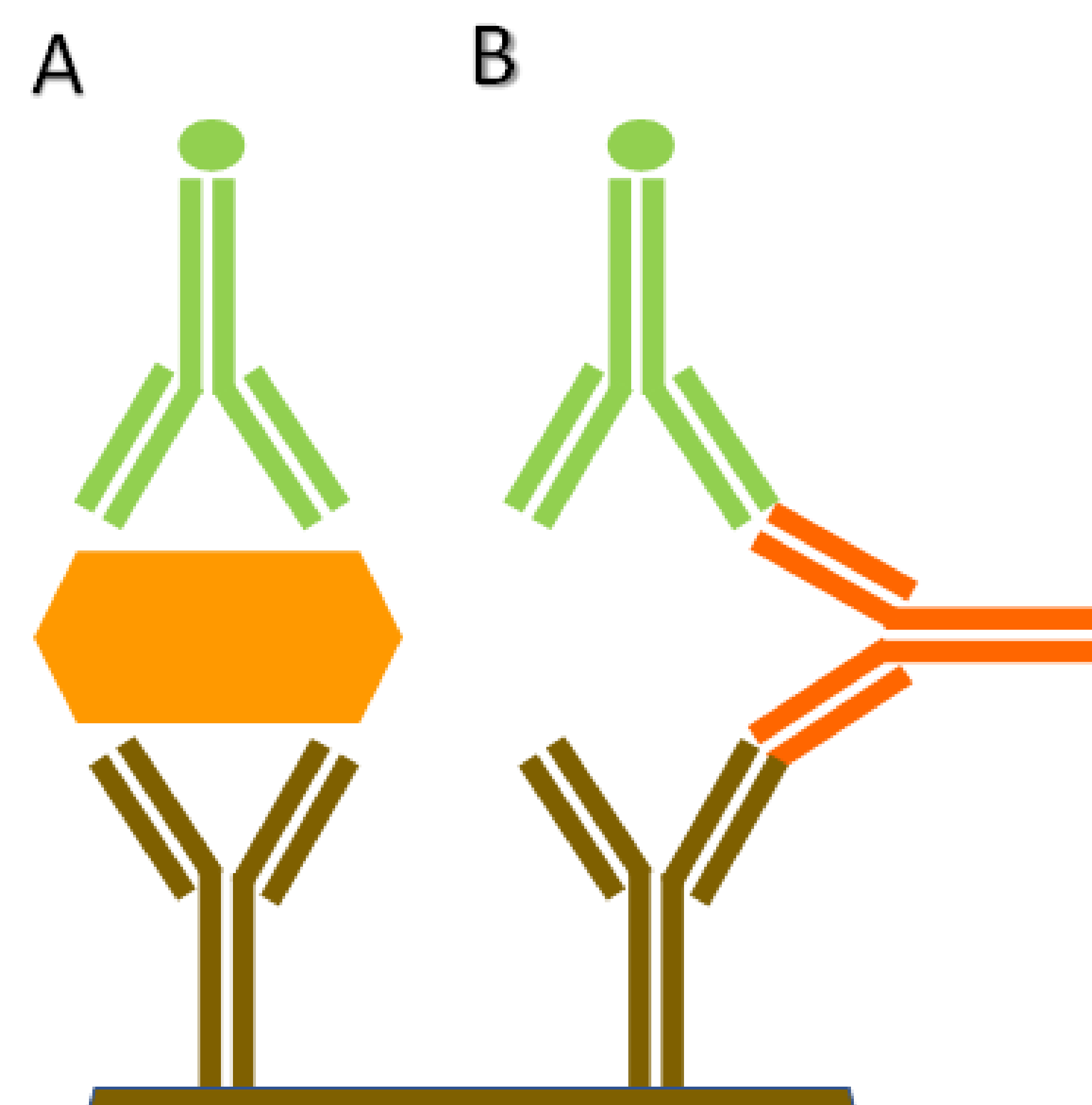
- Human chorionic gonadotropin (hCG) is comprised of an alpha and beta (specific) subunit. hCG is normally produced by the trophoblastic cells of the placenta to maintain early pregnancy. It is also produced in gestational trophoblastic diseases and malignancies (1,2). The terms “pseudohypergonadotropinemia” or “phantom hCG” have been assigned to erroneous hCG detections not clinically correlated to pregnancy or malignancy (2,1).
- Immunoassays are widely used for detection and quantification of analytes in clinical samples. The suggested prevalence of interference in immunoassays ranges between 0.05 to more than 2% (5).
- Non-hCG interfering endogenous antibodies consist of specific anti-animal antibodies (mouse, bovine, porcine, rat, or goat), autoantibodies formed against one of the body’s own proteins (autoimmunity), and heterophilic antibodies which can be either of the aforementioned but less specific and therefore can bind unpredictably and to numerous antigens. These interfering antibodies bind to the immunoassay in the presence or absence of the true analyte, creating an improper signal. It has been suspected that heterophilic antibodies are present in approximately 30-40% of the population and develop through environmental exposures (2).
- Rheumatoid factor (RF), an autoantibody to the Fc constant domain of IgG, has been a suspected cross-reactive analyte. RF is present in low concentrations in approximately 5% of the general population and 70% of rheumatoid arthritis and some other connective tissue disorders (3) including patients afflicted with juvenile idiopathic arthritis (JIA).

Case

- 16-year-old female with a diagnosis of polyarticular JIA
- Initially presented at age 13 with left hip effusion, MCP & PIP synovitis, elevated inflammatory markers, and positive autoantibodies (RF 1280 IU/mL, CCP >300 IU/mL).
- Given erosive changes noted on x-rays of bilateral hands, initiated on a TNF alpha inhibitor therapy. After 6 months of treatment with improved but continued arthritis, methotrexate was added.
- Following routine laboratory monitoring while on methotrexate, the patient’s serum qualitative hCG resulted positive (StanbioQuPID Plus One Step Pregnancy Test), leading to immediate cessation of methotrexate and urgent appointment arranged with patient’s PCP, who practiced through a neighboring health system.
- Subsequent serum qualitative hCG ordered through patient’s PCP resulted negative (Siemens ADVIA Centaur XP Immunoassay System Total hCG Assay), 9 days after original positive.
- Patient denied any prior sexual activity and had regular menses on combined OCPs started for a history of dysmenorrhea through OBGYN.
- Further workup was completed by OBGYN including prolactin, TSH, Monospot, and transabdominal pelvic ultrasound. All unremarkable.
- Lab inquiry was placed. It was recommended to recheck a serum qualitative hCG as well as a serum quantitative hCG. This resulted again in a positive qualitative but undetectable quantitative test. The same blood sample was treated with heterophilic blocking agent (Scantibodies Laboratory Inc Heterophilic Blocking Tube) which when assayed again, resulted a negative serum qualitative hCG.
- Given patient’s active synovitis, elevated serum inflammatory markers, and unclear methotrexate compliance given gaps in pharmacy fill history, there were concern that patient was in an acute inflammatory state with increased circulating autoantibodies when the serum qualitative hCG was drawn.

Discussion

- Clinicians should be attentive to test results deviating from the clinical picture as well as communicating with the analyzing laboratory if there is suspicion of error. Important clinical decisions may be made based on spurious results.
- Numerous prior studies have cited RF as the cause of immunoassay interference (6,7,8). Our patient had a high RF titer.
- Erroneously elevated hCG detection can be a hazard to patient safety, delay appropriate treatment, be psychologically taxing, or lead to unnecessary invasive or costly work up. In our case for example, the patient had known erosive joint changes which could have progressed and impaired future functioning while treatment was held. She underwent several blood draws, imaging, and emotional distress.
- Heterophilic antibodies are large glycoproteins that are filtered by the glomerulus while hCG is freely excreted into the urine (2). Therefore, urine pregnancy tests should not have similar heterophilic antibody interference.
- Further research is needed on characterizing specific heterophilic antibodies/commonly known and clinically relevant rheumatologic antibodies by manufacturers and clinical laboratories to develop strategies for preventing and managing immunoassay interference.
- In our rheumatology clinic, we have chosen to recommend obtaining a urine pregnancy test rather than a serum hCG for screening.



Schematic illustration of the “sandwich” principle of immunoassay

Capture antibody – Binds antigen = hCG beta unit. Monoclonal anti-hCG. Fixed to immunoassay.

Tracer/Sensor antibody - Monoclonal or polyclonal. Labeled with enzyme, dye, or radioactive substrate.

Antigen – Targeted substrate. hCG (A)

Heterophilic antibody – Binds and creates signal, RF (B).

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