Not All Measured Progesterone is Secreted by the Corpus Luteum

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Background

Clinical Necessity
- Accurate progesterone measurement is essential for critical decision-making in assisted reproductive technology cycles
- Immunoassays are the most widely used tool for rapid hormone quantification in clinical settings
- Spironolactone is a common medication for acne and hirsutism that shares structural homology with progesterone

Limitations / Risk of Error
- Assays are susceptible to cross-reactivity from compounds that are structurally similar to endogenous steroids
- Cross-reactivity can generate spurious results, leading to incorrect clinical assessments

Novel Findings
- We performed a comprehensive survey of the literature and found no previous documentation of this specific interference in IVF patients
- This is the first report of persistently elevated P4 levels solely attributed to spironolactone use prior to an ART cycle

Objectives

To evaluate a case of prolonged elevated progesterone levels, the differential diagnosis and to discuss clinical implications

Materials and Methods

Patient
27-year-old nulligravid female undergoing elective oocyte cryopreservation

Medical History

Acne Vulgaris
- Spironolactone 150mg daily for > 1 year

Ankylosing Spondylitis
- Celecoxib
- Adalimumab

Labs

8/15/23 AMH 0.22 ng/mL
9/30/24 AMH 0.14 ng/mL, FSH 20 mIU/mL, E2 35 pg/mL
11/18/24 AMH 0.07 ng/mL

Results

Patient Status & Medication Adherence
- **Baseline Status:** Prior to the intended ovarian stimulation, the patient presented with secondary amenorrhea
- **Physiological Context:** The absence of menses from March 6, 2025 – June 19, 2025 was clinically attributed to her levonorgestrel IUD (Mirena).
- **Medication Continuity:** The patient maintained strict adherence to her spironolactone use for acne therapy prescribed by her primary care provider until August 2025.

Detection of Anomalous Levels
- **Monitoring Shift:** Due to a logistical delay in starting the stimulation cycle, monitoring was temporarily shifted from the office setting to a hospital-based laboratory (SHC) for patient convenience
- **The Discrepancy:** While monitoring at the SHC facility, progesterone (P4) levels were consistently in the low luteal range, inconsistent with the patient's clinical anovulatory picture
- **Duration of Error:** These elevated levels persisted for 24 documented days.

Confirmation of Assay Interference
- **Investigation:** To rule out physiological causes, the patient was recalled to the office (OF) for repeat testing
- **Office Results (OF):** Samples processed in the office laboratory consistently returned low/baseline P4 levels, confirming the patient was in the follicular phase. Intermittent hCG testing confirmed the absence of pregnancy. The low OF levels can be attributed to an adrenal source for P4.
- **Reproducibility:** When labs were subsequently drawn again at the hospital (SHC), the P4 levels returned to the luteal range
- **Conclusion of Testing:** This differences between P4 levels at the two facilities strongly indicated the assay as the source of error. There is unlikely to have been cross reactivity between the patient's levonorgestrel IUD and progesterone assay as progesterone immunoassays are designed with antibodies specific to progesterone and show minimal cross-reactivity with synthetic progestins.

Date	Site	E2 (pg/mL)	P4 (ng/mL)	Comments
3/6/25	OF	17	0.3	
5/6/25	SHC	46	3.1	hCG <1 mIU/mL
5/13/25	SHC	37	2.4	
5/22/25	SHC	29	3.3	hCG <1 mIU/mL
5/29/25	SHC	39	2.7	
6/6/25	OF	58	0.4	
6/19/25	SHC	26	2.7	

Conclusion

Mechanism of Interference
- A review of the literature confirms that canrenone, an active metabolite of spironolactone, acts as a structural mimic of progesterone, leading to significant cross-reactivity on susceptible immunoassay platforms
- The Abbott Architect i2000 system used at SHC has a documented susceptibility to this metabolite, particularly when measuring progesterone in the lower physiological ranges
- In contrast, the Roche Cobas e601 immunoassay used in the office setting demonstrated high specificity with no cross-reactivity, yielding accurate baseline results despite the presence of spironolactone

Non-Interchangeability
- This case highlights a critical limitation in laboratory standardization
- Progesterone values obtained from different immunoassay platforms are not directly comparable and cannot be used interchangeably during treatment monitoring

Clinical Implications
- The artifactual elevation of progesterone led to the inappropriate delay of this patient's ART cycle and necessitated a costly, time-consuming diagnostic workup to clear her for stimulation

Medication induced assay interference must be considered in the differential diagnosis whenever steroid measurements are discordant with the patient's clinical presentation

References

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