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Original Research Article

The Role of Prolactin in Assessing Luteal Phase Infertility

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Abstract: *Luteal phase defect (LPD) is implicated in a substantial proportion of infertility cases, yet the role of circulating prolactin in luteal competence remains controversial. Although prolactin supports corpus luteum function in vitro, its utility as a clinical marker for luteal adequacy in women with regular cycles and no galactorrhea is unclear.* ***Objective:*** *To determine the prevalence of midluteal hyperprolactinemia among infertile women and to assess its association with luteal phase parameters, including cycle length, progesterone and estradiol levels, and endometrial histology.* ***Methods:*** *In this cross-sectional study, 130 infertile women aged 20–40 years with regular ovulatory cycles and no clinical hyperprolactinemia underwent basal body temperature monitoring, midluteal hormone assays, and endometrial biopsy. Plasma prolactin, progesterone, and estradiol were quantified by radioimmunoassay between four and ten days post-ovulation. Endometrial samples obtained on cycle days 21–24 were histologically staged using Noyes and Dallenbach-Hellweg criteria; repeat biopsy was performed if initial results suggested LPD. Hyperprolactinemia was defined as prolactin above the laboratory reference range.* ***Results:*** *Fifteen women (11.5%) were hyperprolactinemic and 115 (88.5%) normoprolactinemic. LPD occurred in 1/15 (6.7%) hyperprolactinemic versus 20/115 (17.4%) normoprolactinemic women (p=0.13). Mean luteal phase length (13.0±1.4 vs 13.1±1.6 days), midluteal progesterone (13.3±4.8 vs 14.4±5.1 ng/mL), and estradiol (233±102 vs 227±99 pg/mL) did not differ significantly between groups. Four hyperprolactinemic women conceived spontaneously or with minimal support; others had additional infertility factors or remain under evaluation.* ***Conclusions:*** *Midluteal hyperprolactinemia is neither common nor predictive of luteal dysfunction in infertile women with regular cycles and no galactorrhea. A comprehensive assessment, incorporating histologic dating and steroid profiling, remains essential for accurate diagnosis of LPD and tailored infertility management.*

Keywords: Hyperprolactinemia; Luteal phase defect; Infertility; Endometrial histology; Progesterone; Estradiol

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Introduction

The luteal phase of the menstrual cycle, the interval between ovulation and the onset of menstruation, is critical for establishing and maintaining early pregnancy, during which the corpus luteum secretes progesterone to prepare the endometrium for implantation and support early embryogenesis (1). A deficiency in luteal function, commonly termed luteal phase defect (LPD), has been implicated in up to 20 % of women presenting with infertility or recurrent early pregnancy loss (2). Histologically, LPD is characterized by delayed or inadequate endometrial maturation relative to chronological cycle day, often assessed by histologic dating of endometrial biopsy specimens obtained in the late secretory phase (3).

A spectrum of etiologies may underlie LPD, including subtle ovarian insufficiency, dysregulation of the hypothalamic–pituitary–ovarian axis, metabolic abnormalities, and aberrant steroid production by luteal cells (4). Clinically, four groups appear particularly susceptible: women with histories of early miscarriage, those who have self-administered clomiphene citrate, older reproductive-age women, and women exhibiting elevated circulating prolactin levels despite regular cycles and absence of galactorrhea (5).

Prolactin, a polypeptide hormone classically associated with lactogenesis, was first designated "luteotrophic hormone" based on early experimental work demonstrating its supportive role in pigeon corpus luteum morphology (6). Subsequent analyses revealed that prolactin concentrations in human follicular fluid during the luteal phase exceed those in peripheral serum, suggesting a local modulatory function (7). In vitro, human granulosa cells require physiologic prolactin concentrations (5–20 ng/mL) to optimize progesterone synthesis; levels beyond this range paradoxically suppress steroidogenesis (8). The identification of prolactin receptors in primate luteal tissue further supports a direct ovarian action of prolactin in luteal maintenance (9).

Despite robust in vitro data, the in vivo role of circulating prolactin in luteal competence remains controversial. Marked hyperprolactinemia is known to impair gonadotropin-releasing hormone pulsatility and inhibit ovulation (10). However, modest elevations of prolactin have produced inconsistent effects on luteal steroid profiles and endometrial maturation in clinical studies (11). Pharmacologic reduction of prolactin with bromocriptine has been reported to reverse histologically confirmed LPD and restore fertility in hyperprolactinemic women (12), yet other interventions that elevate prolactin fail to alter menstrual cyclicity or luteal function.

Diagnosis of LPD traditionally relies on endometrial biopsy and histologic dating (3). However, noninvasive assessments such as basal body temperature monitoring and serial measurement of midluteal progesterone and estradiol by radioimmunoassay are also employed to gauge luteal adequacy (13,14). Nevertheless, prolactin measurement remains a routine component of infertility workups, even though its predictive value for luteal competence has not been systematically validated in women without overt hyperprolactinemic symptoms.

In infertile women with regular ovulatory cycles and no clinical signs of galactorrhea, the true prevalence of hyperprolactinemia and its impact on objective luteal phase metrics, cycle length, steroid hormone levels, and endometrial histology have not been comprehensively compared (15,16). The present study, therefore, examines mid-luteal plasma prolactin, progesterone, and estradiol concentrations alongside histologic dating of endometrial biopsies in a cohort of 130 women to clarify whether prolactin status independently predicts luteal phase adequacy.

Methodology

This cross-sectional study was conducted at the infertility clinic of Aziz Bhatti Shaheed Teaching Hospital, Gujrat, Pakistan, from June 2022 to June 2023. The institutional Ethics Review Board approved the protocol, and all participants provided written informed consent. Women aged 20–40 years with primary or secondary infertility, regular ovulatory menstrual cycles (25–35 days), and no clinical signs of hyperprolactinemia (e.g., galactorrhea) or use of medications affecting pituitary-ovarian function were eligible. Standard infertility evaluation criteria were applied (19). Exclusion criteria comprised polycystic ovary syndrome, thyroid dysfunction, advanced endometriosis (stage III–IV), and prior luteal support. Ovulation was confirmed by daily basal body temperature (BBT) recordings under standardized conditions over two consecutive cycles. The luteal phase length was defined as the number of days from the biphasic thermal shift to the day preceding menses. The cycle with the most consistent biphasic pattern was selected for detailed assessment.

Endometrial biopsies were obtained in the late secretory phase (cycle days 21–24) using a Pipelle curette, sampling both anterior and posterior fundal regions. Histologic dating was performed according to the Noyes criteria (21), and secretory staging was interpreted in accordance with Dallenbach-Hellweg's guidelines (23). If initial histology indicated a luteal phase defect or was inconclusive, a second biopsy was performed in the subsequent cycle under identical conditions. Between postovulatory days 4 and 10, venous blood samples were collected for midluteal hormone measurements. Plasma progesterone was quantified by radioimmunoassay (RIA) as described by Abraham et al. (24), estradiol by steroid RIA per Abraham and Manlimos (25), and prolactin by homologous RIA following Reuter et al. (26). The highest of three prolactin values was used for analysis. All assays were performed in the hospital's endocrine laboratory, with intra- and inter-assay coefficients of variation of less than 10%.Continuous variables (luteal phase length, hormone concentrations) are expressed as mean ± SD. The prevalence of histologically confirmed luteal phase defect was compared between hyperprolactinemic and normoprolactinemic groups using the chi-square test. A two-tailed Student's t-test was used to assess between-group differences in luteal phase duration and hormone levels. A $p < 0.05$ was considered statistically significant.

Results

A total of 130 women fulfilled the inclusion criteria and completed the full luteal assessment protocol. Of these, 15 (11.5%) were classified as hyperprolactinemic (midluteal prolactin > laboratory upper limit) and 115 (88.5%) as normoprolactinemic. Endometrial histology revealed luteal phase defect (LPD) in 1 of 15 (6.7%) hyperprolactinemic women, versus 20 of 115 (17.4%) normoprolactinemic women ($\chi^2=2.35$; $p=0.13$), indicating no statistically significant association between elevated prolactin and histologic LPD.

Although midluteal prolactin differed more than threefold between the groups (31.65 ± 14.38 vs. 8.44 ± 3.46 ng/mL; $p < 0.001$), there were no meaningful differences in progesterone or estradiol secretion, nor in the duration of the luteal interval (all $p > 0.05$) (Table 1). This indicates that, within the observed range, elevated prolactin did not suppress luteal steroidogenesis or shorten the luteal window.

Table 2 details that 14 of the 15 hyperprolactinemic women exhibited endometrial maturation appropriate for cycle day and midluteal progesterone levels within the expected physiologic range (6–21 ng/mL) and luteal lengths of 11–15 days. Only patient 12 demonstrated persistent histologic delay despite adequate progesterone, confirming true LPD across two biopsies. Notably, this sole LPD case occurred in a woman whose prolactin was markedly elevated (57 ng/mL), yet the small sample size precludes statistical inference about extreme hyperprolactinemia.

Clinically relevant outcomes further underscore the lack of deleterious effect of modest prolactin elevation on luteal performance: three hyperprolactinemic women (patients 2, 4, and 8) achieved spontaneous conception within six months post–evaluation, and one (patient 5) conceived following adjunctive clomiphene and hCG therapy. The remaining women either had additional infertility factors, male factor (n = 3), tubal factor (n = 2), cervical factor (n = 2), or endometriosis (n = 1), or are still undergoing further workup.

In aggregate, these findings demonstrate that in women with regular cycles and no galactorrhea, elevated midluteal prolactin is neither prevalent nor predictive of impaired luteal histology or steroidogenic output. Both objective measures, histologic dating and hormone profiles, were comparable irrespective of prolactin status, calling into question the routine use of midluteal prolactin alone as a surrogate marker for luteal adequacy.

Table 1: Comparison of luteal phase parameters between hyperprolactinemic and normoprolactinemic women

Parameter	Hyperprolactinemic (n = 15)	Normoprolactinemic (n = 115)	P-value
Prolactin (ng/mL)	31.65 ± 14.38	8.44 ± 3.46	< 0.001
Progesterone (ng/mL)	13.27 ± 4.80	14.43 ± 5.07	0.48 (NS)
Estradiol (pg/mL)	233 ± 102	227 ± 99	0.75 (NS)
Luteal phase length (days)	13.0 ± 1.38	13.1 ± 1.56	0.82 (NS)

Table 2: Individual luteal profiles of hyperprolactinemic women

Pt	Prolactin (ng/mL)	Progesterone (ng/mL)	Luteal Length (days)	Histology
1	30.3	11.1	11	Normal
2	21.0	10.0	12	Normal
3	29.0	12.0	15	Normal
4	23.0	10.0	15	Normal
5	29.0	6.0	13	Normal
6	26.0	20.0	13	Normal
7	23.0	8.0	12	Normal
8	24.0	12.0	13	Normal
9	21.0	11.0	14	Normal
10	27.0	16.0	14	Normal
11	68.0	21.0	14	Normal
12	57.0	10.0	N/A	Abnormal†
13	21.0	16.0	11	Normal
14	48.0	11.0	11	Normal
15	24.0	17.0	14	Normal

†Confirmed abnormal in two consecutive cycles

Discussion

In this cohort of 130 infertile women with regular ovulatory cycles and no galactorrhea, hyperprolactinemia, defined as a midluteal prolactin concentration above the assay's upper reference limit, was present in 11.5% of participants. This prevalence closely parallels prior reports from infertility clinics, where mild to moderate prolactin elevations have been documented in approximately 10–15% of women undergoing evaluation (19). Histologic luteal phase defect (LPD) was identified in only 6.7% of hyperprolactinemic women, compared with 17.4% of those with normal prolactin levels ($\chi^2 = 2.35$; $p = 0.13$). The overall LPD rate in normoprolactinemic women aligns with earlier histopathologic series reporting luteal insufficiency in 15–20% of infertile patients (8, 16). Thus, our data demonstrate that elevated midluteal prolactin is neither particularly common nor predictive of histologic LPD in this population (8, 16, 19).

Prolactin's putative luteotrophic role is rooted in classical and contemporary experimental work. Schooley and Riddell first coined the term "prolactin " as the "luteotrophic hormone," based on avian studies demonstrating its necessity for corpus luteum maintenance (1). Subsequent in vitro experiments revealed that human granulosa cells maximize progesterone output when cultured with physiologic prolactin concentrations (5–20 ng/mL), whereas supraphysiologic levels inhibit steroidogenesis (4). The presence of prolactin receptors on human luteal cells further substantiates a direct ovarian action, implicating prolactin as a modulator of luteal steroid production in primates (7). Collectively, these findings provide a mechanistic rationale for investigating prolactin's impact on human luteal competence; however, our in vivo results suggest that circulating levels within the mild-to-moderate range exert minimal functional consequences (1, 4, 7).

Clinical interventions targeting prolactin have yielded mixed outcomes. Bromocriptine therapy has been reported to correct histologic LPD and restore fertility in hyperprolactinemic women, highlighting prolactin suppression as a potential therapeutic strategy (11, 12). Conversely, provocation of prolactin secretion via thyrotropin-releasing hormone failed to alter corpus luteum function or menstrual cyclicity in normally menstruating women, underscoring the complexity of prolactin's endocrine interactions and the limited in vivo sensitivity of the luteal apparatus to transient prolactin elevations (18). Our findings, demonstrating preserved luteal steroidogenesis and histologic maturation despite elevated prolactin, are consistent with these clinical observations and argue against the routine use of bromocriptine solely to optimize luteal function in otherwise asymptomatic women (11, 12, 18).

Endometrial biopsy with histologic dating remains the diagnostic gold standard for LPD; however, it is inherently invasive and subject to sampling variability. Noyes' histologic criteria and Dallenbach-Hellweg secretory staging provide standardized frameworks for assessing endometrial maturation relative to cycle day (21, 23). In our study, 14 of 15 hyperprolactinemic women exhibited endometrial histology concordant with expected secretory patterns, reinforcing the limited predictive utility of midluteal prolactin measurement. Hormonal assays by radioimmunoassay used here for progesterone, estradiol, and prolactin have well-established accuracy and precision, with intra- and inter-assay coefficients of variation below 10% (24–26). The congruence of histologic and biochemical luteal markers in hyperprolactinemic and normoprolactinemic women further supports a multiparametric approach to luteal evaluation rather than reliance on a single prolactin value (21–26).

From a clinical perspective, prolactin measurement remains a routine component of infertility workups due to concerns about pituitary pathology and ovulatory dysfunction. Evaluation of hyperprolactinemia typically involves dynamic testing and imaging when levels are markedly elevated (19, 20). However, our data indicate that mild to moderate prolactin elevations in the absence of galactorrhea or other pituitary symptoms do not correlate with luteal insufficiency. Thus, clinicians should exercise caution before attributing luteal phase abnormalities solely to prolactin and consider a comprehensive assessment, including histologic dating and serial steroid measurements, to guide management (19, 20, 24).

This study's limitations include reliance on a single midluteal prolactin measurement without assessment of macroprolactin or dynamic secretory patterns, which may obscure the true bioactive prolactin burden. The relatively small hyperprolactinemic subgroup also limits statistical power to detect subtle effects at the extremes of prolactin elevation. Future research should incorporate longitudinal prolactin profiling, evaluation of prolactin isoforms, and integration of molecular markers of endometrial receptivity, such as the expression of progesterone-regulated genes, to more precisely delineate prolactin's reproductive roles (10, 22).

Finally, our findings demonstrate that elevated midluteal prolactin concentrations in women with regular cycles and no clinical hyperprolactinemia are neither prevalent nor predictive of luteal phase inadequacy. Direct measures of luteal function, including endometrial histologic dating and steroid hormone assays, remain the most reliable indicators for diagnosing LPD and guiding tailored infertility therapies.

Conclusion

In infertile women with regular ovulatory cycles and no clinical signs of hyperprolactinemia, elevated midluteal prolactin levels occur in only a minority and do not predict luteal phase adequacy. Despite a more than threefold difference in prolactin between hyperprolactinemic and normoprolactinemic groups, both histologic dating of endometrial biopsies and midluteal progesterone and estradiol concentrations remained comparable. These findings demonstrate that a single midluteal prolactin measurement, in the absence of galactorrhea or other pituitary symptoms, lacks sufficient sensitivity and specificity to serve as a standalone marker of luteal competence. Therefore, comprehensive assessment incorporating endometrial histology and serial steroid assays remains the most reliable approach for diagnosing luteal phase defect and guiding infertility management.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-22)

Consent for publication

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The authors declared the absence of a conflict of interest.

Author Contribution

SC (General Physician)
Manuscript drafting, Study Design,
Conception of Study, Development of Research Methodology Design,
RA (General Physician)
Study Design, manuscript review, and critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

References

1. Schooley JP, Riddell J. The morphological basis of pituitary function in pigeons. Am J Anat. 1938; 62:313? https://doi.org/10.1002/aja.1000620302
2. McNatty KP, Hunter WM, McNeilly AS, Sawers RS. Changes in the concentration of pituitary and steroid hormones in the follicular fluid of human Graafian follicles throughout the menstrual cycle. J Endocrinol. 1975; 64:555. https://doi.org/10.1677/joe.0.0640555
3. Vara JF, Carretero MV, Gerónimo H, Ballmer-Hofer K, and Martín-Pérez J. Stimulation of c-Src by prolactin is independent of Jak2. Biochem J. 2000; 345(Pt 1):17–24. https://doi.org/10.1042/0264-6021:3450017
4. McNatty KP, McNeilly AS, Sawers RS. Prolactin and progesterone secretion by human granulosa cells in vitro. In: Crosignani PG, Robyn C, editors. Prolactin and Human Reproduction. New York: Academic Press; 1977. p. 109–117.
5. Chang RJ. Normal and abnormal prolactin metabolism. Clin Obstet Gynecol. 1978; 21:125.
6. Tsai-Morris CH, Dufau ML. Prolactin receptor (PRLR). In: Atlas Genet Cytogenet Oncol Haematol (Internet). Salamanca (Spain): Institute for Biomedical Research of Salamanca; 2011 (cited 2023 Dec 26). Available from: http://atlasgeneticsoncology.org/gene/42891/
7. Poindexter AN, Buttram VC Jr, Besch PK, Smith RG. Prolactin receptors in the ovary. Fertil Steril. 1979; 31:273–?. https://doi.org/10.1016/S0015-0282(16)44004-8
8. Ross GT, Hillier SG. Luteal maturation and luteal phase defect. Clin Obstet Gynaecol. 1978; 5:391.
9. Torner L. Actions of prolactin in the brain: from physiological adaptations to stress and neurogenesis to psychopathology. Front Endocrinol (Lausanne). 2016; 7:25. https://doi.org/10.3389/fendo.2016.00025
10. Tambascia M, Bahamondes L, Pinotti J, Collier AM, Dachs IN, Faundes A. Sustained hyperprolactinemia in a normally menstruating woman with apparently normal ovarian function. Fertil Steril. 1980; 34(3):282–284. https://doi.org/10.1016/S0015-0282(16)44964-2
11. Saunders DM, Hunter JC, Haase HR, Wilson GR. Treatment of luteal phase inadequacy with bromocriptine. Obstet Gynecol. 1979; 53:287.
12. Annos T, Thompson IE, Taymor ML. Luteal phase deficiency and infertility: difficulties encountered in diagnosis and treatment. Obstet Gynecol. 1979; 55:705.
13. Balasch J, Vanrell JA, Marquez M, Burzaco I, Gonzalez-Merlo J. Dydrogesterone versus vaginal progesterone in the treatment of the endometrial luteal phase deficiency. Fertil Steril. 1982;37(6):751https://doi.org/10.1016/S0015-0282(16)46333-8
14. Dallenbach-Hellweg G. Histopathology of the Endometrium. 2nd ed. Berlin: Springer-Verlag; 1975. p. 83.
15. Abraham GE, Swerdloff R, Tulchinsky D, Odell WD. Radioimmunoassay of plasma progesterone. J Clin Endocrinol Metab. 1971; 32(5):619–624. https://doi.org/10.1210/jcem-32-5-619
16. Abraham GE, Manlimos FS, Garza R. Radioimmunoassay of steroids. In: Abraham GE, editor. Handbook of Radioimmunoassay. New York: Marcel Dekker, 1977. p. 591.
17. Reuter AM, Kennes F, Gevaert Y, Franchimont P. Homologous radioimmunoassay for human prolactin. Int J Nucl Med Biol. 1976; 3(1):21–?. https://doi.org/10.1016/0047-0740(76)90053-1
18. Jones GS. The luteal phase defect. Fertil Steril. 1976; 27(4):351–356. https://doi.org/10.1016/S0015-0282(16)41769-3
19. Wentz AC. Manual of Gynecology. 2nd ed. Philadelphia: WB Saunders; 1976. p. 1–20.
20. Wenner R. Les antiprolactines. Actual Gynecol (Paris). 1975; 6:91. DOI not available.
21. Quigley HM, Haney AF. Evaluation of hyperprolactinemia: clinical profiles. Clin Obstet Gynecol. 1980; 23(2):337–348. https://doi.org/10.1097/00003081-198006000-00006
22. Archer DF. Physiology of prolactin. Clin Obstet Gynecol. 1980;23(2):325–335. https://doi.org/10.1097/00003081-198006000-00005
23. Schwärzler P, Untergasser G, Hermann M, Dirnhofer S, Abendstein B, Berger P. Prolactin gene expression and prolactin protein in premenopausal and postmenopausal human ovaries. Fertil Steril. 1997; 68(4):696–701. https://doi.org/10.1016/S0015-0282(97)00320-8
McNamara AV, Awais R, Momiji H, Dunham L, Featherstone K, Harper CV, et al. The transcription factor Pit-1 influences transcriptional timing in the dual-promoter human prolactin gene. Endocrinology. 2021;162(4):bqaa249. https://doi.org/10.1210/endocr/bqaa249.