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Review

Progesterone as a Prognostic Biomarker for Expectant Management of Tubal Ectopic Pregnancy: A Narrative Review

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Abstract

Background/Objectives: Tubal ectopic pregnancy (TEP) remains a significant cause of maternal morbidity and mortality. Early access to pregnancy assessment units now allows for the detection of many TEPs at a stage at which they could potentially resolve spontaneously. The current selection of women for expectant management is guided by human chorionic gonadotrophin (hCG) concentrations, alongside ultrasonographic and clinical features, although reported success rates vary widely in the literature. We evaluated whether progesterone, another biomarker secreted during pregnancy, can predict successful expectant management alone or in combination with hCG. Methods: A narrative review was undertaken using Ovid MEDLINE and Embase, searched from 1 January 1990 to 1 May 2026, with a supplementary grey literature search. Of 1363 records identified, 27 studies were included. Results: Progesterone is associated with pregnancy viability but performs poorly in isolation for distinguishing ectopic from non-ectopic pregnancy. However, in studies of expectant management success, it has been identified as a second-tier variable that may improve prediction of successful expectant management of TEP. Conclusions: Current evidence does not support the use of progesterone as an independent predictor of expectant management success. It may provide additional prognostic information within an hCG-defined stratum, but this requires further validation before implementation in clinical practice.

Keywords: tubal ectopic pregnancy; ultrasound examination; expectant management; progesterone; hCG

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1. Introduction

1.1. Hormonal Regulation of Periconception and Early Pregnancy

Successful conception and establishment of a normal intrauterine pregnancy depend upon a tightly orchestrated hormonal axis and immunological response. Pulsatile gonadotrophin-releasing hormone (GnRH) drives the release of follicle-stimulating hormone (FSH) and luteinising hormone (LH), which in turn govern follicular development, ovulation and corpus luteum function [1]. Successful conception occurs after ovulation, fertilisation and implantation. Following implantation, the syncytiotrophoblast releases human chorionic gonadotrophin (hCG), which supports the corpus luteum and promotes trophoblast invasion and placentation [2]. The corpus luteum releases progesterone which becomes the dominant steroid hormone of early gestation, playing a major role in creating

a receptive endometrium and maintaining early pregnancy. This is until approximately 7–9 weeks' gestation, when placental progesterone production becomes dominant [3].

Oestradiol, relaxin, and inhibin play complementary roles, but hCG and progesterone remain the two principal hormones and are the biomarkers most commonly measured in clinical practice for the assessment of early pregnancy viability and location [4].

1.2. Tubal Ectopic Pregnancy

The majority of conceptions implant within the uterine cavity and develop as normally sited intrauterine pregnancies. However, a minority of pregnancies implant outside the endometrial cavity, termed ectopic pregnancies [5]. More than 95% of ectopic pregnancies occur in the fallopian tube—while only a minority implant on the cervix, myometrial wall, the ovary, the abdomen or within a caesarean section scar [6]. Ectopic pregnancies affect 11 in 1000 pregnancies in the United Kingdom [7]. Although outcomes in the management of tubal ectopic pregnancy (TEP) have improved significantly over the years, there remains a morbidity and mortality rate of 0.2 per 1000 ectopic pregnancies [7]. In recent decades, increased access to early pregnancy ultrasound and improved sonographic resolution has led to TEP being diagnosed more often and at an earlier gestational stage. This includes women who are asymptomatic and a range of other clinical presentations, including cases that may also resolve spontaneously [8,9]. The clinical challenge is to distinguish those pregnancies which will resolve without complication from those which will progress and cause tubal rupture, leading to significant intra-abdominal bleeding, haemodynamic compromise and death. Even in the absence of rupture, TEP is associated with significant morbidity due to its implications for future fertility and the psychological sequelae for woman [10].

Currently, ultrasound is the cornerstone for the diagnosis of TEP. There are three treatment options for TEP, including surgical management, either by removing the affected tube (salpingectomy) or removing the pregnancy while preserving the tube (salpingostomy), medical management with methotrexate, or expectant management (watchful waiting with serial monitoring of clinical symptoms and hCG) [7]. Clinicians use a range of parameters to counsel patients appropriately and guide treatment decisions, including ultrasound findings and levels of key pregnancy hormones such as hCG and progesterone [11]. Management decisions are informed principally by the prognostic value of serum hCG, ultrasound findings and clinical status. The literature supporting the clinical use of hCG as a prognostic marker is extensive, such as when monitoring for resolution of an expectantly managed TEP, or in establishing discriminatory thresholds for surgical management [12–14]. However, the role of progesterone in TEP management is less well established but recognised as an adjunct and is the focus of this review.

1.3. Patient Perspectives on Management Options

An important component of decision-making is patient preference. Capmas et al. explored this issue in a qualitative project using a discrete choice experiment [15]. Women of childbearing age were recruited ($N = 178$) and asked to choose between hypothetical treatments across 18 choice tasks [15]. Using a conditional logit McFadden's choice model, the authors weighted participants' preferences and identified the factors that most strongly influenced decision-making [15]. In order of importance, participants preferred a higher likelihood of first-line treatment success, a lower risk of tube removal, a lower likelihood of requiring surgery, and shorter hospitalisation. Additionally, though less influential, preferences included shorter recovery time, avoidance of emergency care during convalescence, and lower treatment costs [15]. Although out of the scope of this review, patient preference plays an important role in the uptake and success of management option of TEP. This

highlights the need for shared decision-making supported by local data on management outcomes when counselling women on early pregnancy management options.

1.4. Aims of Review

Progesterone has traditionally not been used as a stand-alone biomarker to predict the likelihood of expectant management success when triaging TEP. However, it has been proposed as an adjunct. In this review, we examine whether progesterone also merits renewed consideration as a prognostic biomarker in the expectant management of TEP.

The use of serum progesterone across different clinical settings in early pregnancy is well established but the particular emphasis on its utility in predicting successful expectant management of TEP is less studied. We aim to distinguish its application from other contexts in which progesterone has been studied, namely the assessment of pregnancy viability, the evaluation of pregnancy of unknown location (PUL) and the prediction of methotrexate treatment outcomes [12,16–20]. We will also critically assess whether evidence supporting progesterone as a marker of non-viability can be extrapolated to predict spontaneous resolution and safe expectant management of confirmed TEP [21].

To achieve our aim, we will consider whether the use of progesterone can address two clinically important questions:

1. Can progesterone predict successful expectant management in tubal ectopic pregnancy?
2. Does progesterone add prognostic value to hCG in the expectant management of tubal ectopic pregnancy?

2. Materials and Methods

For our narrative perspective, we have conducted a search using Ovid where the databases MEDLINE and EMBASE were included. The search was conducted for papers published between 1 January 1990 and 1 May 2026, which was the date of the last search. Abstract-only publications were excluded because their limited peer-review process did not meet the eligibility standard applied to full-text articles. No further searches were run after this date and studies published after 1 May 2026 were not screened. We are not aware of any further studies published after this date that would alter the conclusions of this review. There was no limit regarding the methodology of the papers reviewed, whether they be systematic review or cohort studies. The keywords used in the search specifically looking at literature surrounding progesterone were

- "Serum progesterone" OR "Progesterone" OR "P4";
- "Ectopic" OR "tubal ectopic" OR "TEP";
- (prognos*) OR (triag*) OR (utili*) OR (effective*) OR (screen*) OR (outcome*) OR (expectant) OR (conservative) OR (resolution) OR (miscarr*).

Following this, a grey literature search was conducted with the same keywords using Google Scholar, with key emphasis on institutional guidelines such as the National Institute for Health and Care Excellence (NICE). Studies were selected based on title and abstract screening and collated using Endnote Online reference software manager. Key papers were sorted and included based on their commentary on basic sciences or as clinical evidence. Papers were excluded if they were not in English, published before 1990, poster or conference abstracts, or studies that solely investigate or incorporate assisted reproductive technologies. A flowchart showing identification and selection is summarised in Figure 1. A total of 1363 papers were identified following the database search. Following removal of 234 duplicates, a single reviewer screening of abstracts and full texts was conducted, leaving 27 eligible studies for review and incorporation to our narrative review. As most

papers identified and included in our analysis were non-randomised quantitative studies and comprised a variety of study designs, the Mixed-Methods Appraisal Tool was used to streamline appraisal of included studies in this review. A table of this assessment is presented as Supplementary Table S1.

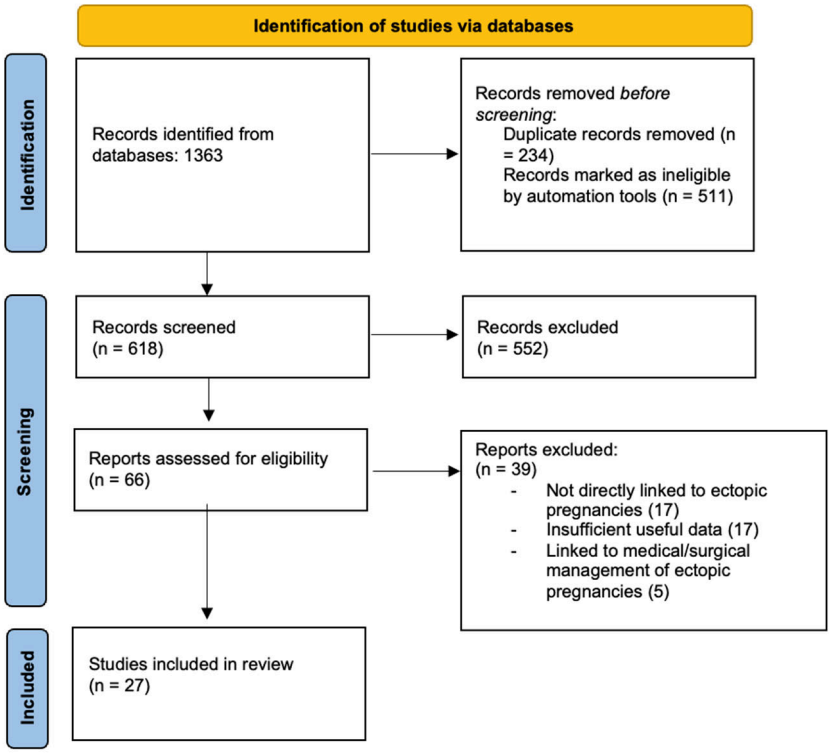


Figure 1. Flowchart showing the identification and selection of studies. Records were identified through searches of Ovid MEDLINE and EMBASE, as described in Section 2. Of 1363 records, 234 duplicates were removed and a further 511 records were excluded by database filters before screening, leaving 618 records for title and abstract screening. Of these, 552 were excluded. Sixty-six full-text reports were assessed by a single reviewer, of which 39 were excluded because they were not directly related to ectopic pregnancy, contained insufficient relevant data, or concerned medical or surgical management. A final 27 studies were included in the review. The diagram is presented in a PRISMA-style format to document the search transparently; however, this is a narrative rather than a systematic review. No protocol was registered, screening was undertaken by a single reviewer, and the included studies were appraised using the Mixed Methods Appraisal Tool, as reported in Supplementary Table S1.

Progesterone concentrations are reported throughout in nmol/L as the primary unit, with values in ng/mL shown in parentheses where reported in the original study; the approximate conversion used is 1 ng/mL = 3.18 nmol/L. Converted values are rounded appropriately and presented consistently. Serum hCG is reported in IU/L.

3. hCG

3.1. Use of hCG and Ultrasound Findings to Triage and Manage Tubal Ectopic Pregnancy: Initial Assessment and Treatment Selection

Selection among expectant, medical and surgical management for TEP is principally guided by serum hCG concentration, the presence or absence of an adnexal mass and free fluid on transvaginal ultrasound, symptom burden and haemodynamic status [7]. Surgical management is generally considered when hCG levels are high, the patient is haemodynamically unstable or when expectant or medical management has been unsuccessful.

3.2. Clinical Triage Criteria and Biological Rationale for hCG-Based Assessment

hCG broadly reflects trophoblastic quantity and activity. Figure 2 outlines the physiology of hCG in a normal intrauterine pregnancy and in TEP. hCG is secreted by the syncytiotrophoblast from implantation, is detectable in maternal serum from 8 days of fertilisation, rises steeply during the first trimester and peaks at 8–10 weeks' gestation. In TEP, higher hCG levels often indicate a more active or persistent ectopic pregnancy that is less likely to regress spontaneously and more likely to require intervention, although exceptions have been reported at very high levels [22].

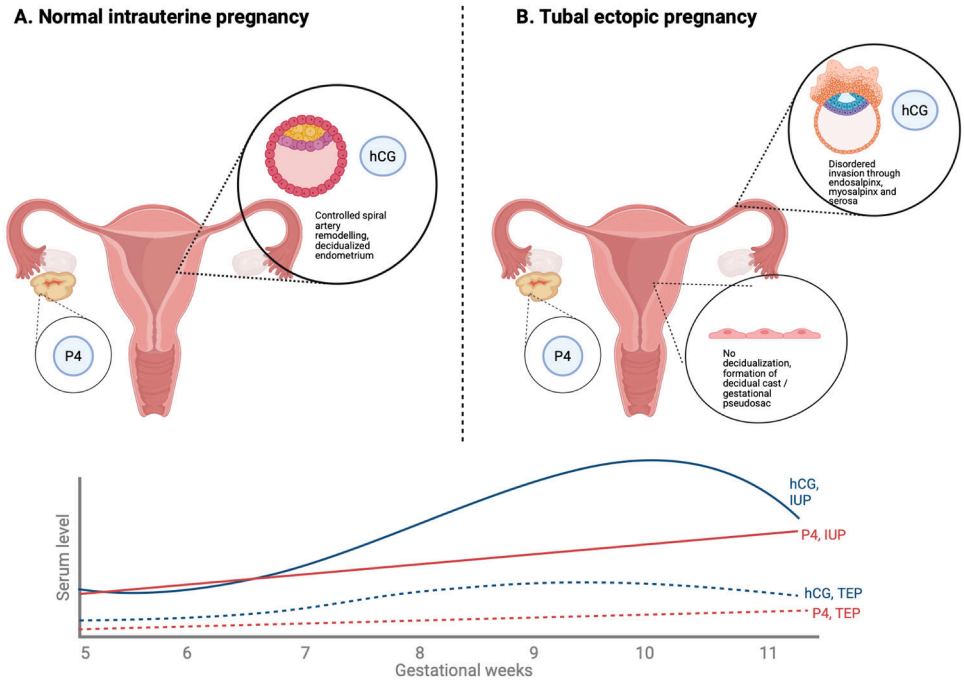


Figure 2. Schematic of the physiology of human chorionic gonadotrophin (hCG) and progesterone in normal intrauterine pregnancy (**A**) and tubal ectopic pregnancy (**B**). In a normally implanted pregnancy, syncytiotrophoblast-derived hCG sustains the corpus luteum, which in turn produces progesterone; both biomarkers reflect overlapping but distinct dimensions of trophoblast activity. In a tubal ectopic pregnancy, aberrant implantation at the tubal site is associated with reduced trophoblast mass and disordered invasion of the endosalpinx, myosalpinx and serosa, with absent decidualisation at the implantation site and characteristically lower serum progesterone. It is hypothesised that hCG indexes the quantity of viable trophoblast; progesterone indexes its function and the integrity of luteal support. The hormone concentration curves are illustrative and not drawn to scale. Source: Created in BioRender. Ahmad, A. (2026). https://BioRender.com/e2w1mfy (accessed on 28 October 2026).

3.3. The Complementary Diagnostic Role of Transvaginal Ultrasound in hCG-Based Assessment

The combination of a positive hCG and the sonographic visualisation of a tubal or adnexal mass is diagnostic of an ectopic pregnancy. However, in isolation, a single hCG measurement alone has no predictive value in determining the likelihood of an ectopic pregnancy, or its size [23].

3.4. Prediction of Treatment Requirements and Clinical Outcomes in the Non-Surgical Management of Tubal Ectopic Pregnancy

In visualised ectopic pregnancies, both single and serial hCG measurements have been investigated as predictors of the likelihood that surgical management will ultimately be required. This includes Al Sayed et al.'s use of hCG to predict future tubal occlusion and therefore suggests a negative impact on future reproductive health and increased recurrence

of ectopic pregnancy with potential surgery. Their observation was of significance in women who completed expectant or medical management of TEP where hCG levels had reached 5000 IU/L or higher. Potter et al. retrospectively used absolute hCG to predict methotrexate treatment success without further intervention in TEP management. Aiob et al. and Orozco et al. recognised that dynamic hCG changes could predict tubal rupture or failure of methotrexate treatment and therefore the need for further intervention and Cohen et al.'s used both dynamic and absolute hCG levels to likewise predict rupture of TEP after methotrexate, necessitating further intervention by surgery [24–28]. Current NICE guidance recommends surgery as first-line management for TEP when serum hCG concentration is 5000 IU/L or greater [7,12].

3.5. Evidence Limitations and Uncertainty in Non-Surgical Management

Decision points for initiating expectant or medical management remain the area of practice least well supported by evidence. A meta-analysis by Solangon et al. that included two multicentre randomised controlled trials (RCTs) ($N = 152$) together with individual patient data found no difference in treatment success rates between expectant management and methotrexate when a lower hCG threshold of <2000 IU/L was used to stratify treatment allocation (RR 1.16, 95% CI 0.95–1.40) [16]. Similarly, a meta-analysis by Naveed et al. comparing expectant and medical management with methotrexate found both methods were comparable for treatment success [29]. Numerous prospective and retrospective studies have investigated the use of hCG-based predictive algorithms to distinguish between TEPs that are likely to resolve spontaneously without intervention and those that are likely to continue growing, potentially leading to complications such as tubal rupture and internal bleeding [4,30–32]. However, no single model has demonstrated sufficient accuracy or external validation for widespread generalisation to all clinical settings.

4. Progesterone

4.1. The Biological Role of Progesterone in Normal Early Pregnancy Development

Progesterone is a steroid hormone synthesised from cholesterol via pregnenolone. In the non-pregnant individual, it is secreted by the corpus luteum during the luteal phase of the menstrual cycle under the trophic influence of LH. Following fertilisation, the syncytiotrophoblast sustains corpus luteum function through the release of hCG, thereby sustaining progesterone production. Progesterone induces secretory transformation of the endometrium, promotes decidualisation, suppresses myometrial contractility, and modulates the maternal immune response to the semi-allogeneic conceptus [33,34]. From the 7th and 9th week of gestation, the site of progesterone production shifts from the corpus luteum to the placenta, otherwise known as the luteoplacental shift [35].

4.2. Serum Progesterone Trends in Viable Intrauterine Pregnancy

In a healthy singleton intrauterine pregnancy, serum progesterone will show an overall rising trend during the first trimester (Figure 2). The luteoplacental shift is associated with a transient fall in progesterone levels between weeks 6 and 8 with the nadir often during week 7. Thereafter, a progressive incline is seen from week 7 of progesterone in normal pregnancy development. Studies have reported removal of the corpus luteum before week 7 for any reason results in miscarriage, whereas lutectomy after week 9 does not [36]. Reference ranges vary by assay and laboratory, but most healthy ongoing pregnancies have a serum progesterone above 35.8 nmol/L at 5 weeks' gestation, increasing by approximately 10 nmol/L per week [17,36].

4.3. Mechanistic Rationale for Progesterone Assessment in Tubal Ectopic Pregnancy

The rationale for measuring progesterone alongside hCG in TEP is that the two hormones may reflect related but distinct biological processes. hCG provides an indirect measure of viable trophoblastic activity, whereas progesterone may reflect the functional adequacy of luteal support and, potentially, the endocrine conditions required for normal early pregnancy development.

One mechanism described in the literature is luteal phase deficiency. This refers to inadequate progesterone during the luteal phase and early pregnancy and has been associated with an increased risk of intrauterine pregnancy miscarriage. Several mechanisms have been proposed to explain its adverse effect on normal pregnancy development. Ku et al. describe two commonly cited aetiologies: (1) the impaired function of the corpus luteum, resulting in insufficient progesterone and oestradiol secretion, or (2) failure of the endometrium to appropriately respond to raised progesterone and oestradiol levels [36]. In TEP, it is biologically plausible that the abnormal implantation site may contribute to luteal dysfunction or alter endocrine signalling, although the mechanism remains incompletely established.

In viable intrauterine pregnancy, the principal target of progesterone is the endometrium, where it promotes secretory transformation, decidualisation, and regulated trophoblastic invasion [18]. These processes are disrupted in TEP because implantation occurs outside the endometrial cavity. At the tubal implantation site, decidualisation is absent or limited, and trophoblastic invasion may proceed in a disordered manner through the endosalpinx, myosalpinx, and serosa [37]. Consequently, the endometrial response may be uncoupled from pregnancy location and outcome. We suggest that the disordered placentation seen in TEP may underlie non-linear or suboptimal progesterone trajectories. In some cases, these biological patterns may indicate inadequate luteal support or failure of the luteoplacental transition, rather than the coordinated endocrine profile characteristic of normally implanted intrauterine pregnancies.

4.4. Limitations of Progesterone as an Independent Prognostic Marker in Tubal Ectopic Pregnancy

A key limitation is that, before the luteoplacental shift, circulating progesterone is produced predominantly by the corpus luteum under stimulation from hCG [35]. Serum progesterone is therefore biologically linked to hCG. For progesterone to add independent prognostic value in TEP, luteal output would need to vary meaningfully at a given hCG concentration; this has not been demonstrated in the literature reviewed. Prospectively validated models of hCG clearance in expectantly managed TEP have not been identified, and although retrospective data suggest at least two different hCG clearance gradients, they do not reliably predict which ectopic pregnancies will resolve spontaneously [22].

5. Clinical Utility of Progesterone in TEP

5.1. Can Progesterone Predict Successful Expectant Management in Tubal Ectopic Pregnancy?

5.1.1. Factors Influencing Progesterone Interpretation

In the first trimester of a viable pregnancy, serum progesterone concentrations are affected by several maternal characteristics. Four important predictors have been identified: maternal age, body mass index (BMI), gestational age and parity. These predictors need to be considered in assessments of progesterone levels [36]. Obesity, for example, is associated with lower progesterone concentrations. This may reflect two mechanisms: adipocytokine-mediated impairment of corpus luteum function and greater volume of distribution and lower circulating concentrations of progesterone related to its lipid-soluble properties. The same group also highlighted the need for further work to determine whether ethnic variation

in progesterone concentrations exists. Such demographic variations in progesterone of normally sited pregnancies are likely to also in occur in ectopic pregnancies.

5.1.2. Progesterone as a Triage and Diagnostic Marker

Taking this into account, on one hand, isolated studies have shown progesterone to be a useful triage tool in initial management in early pregnancy. Before the widespread availability of ultrasound, progesterone was used in emergency department settings to identify patients with a high likelihood of viable developing pregnancies and to distinguish these from failing pregnancies, with low progesterone concentrations indicating either a failing ectopic pregnancy or a failing intrauterine pregnancy, with good discriminatory capacity [38]. Evidence evaluating progesterone alone for the identification of ectopic pregnancy suggests good sensitivity but poor specificity. Using a lower threshold, as in Dart et al. (<5 ng/mL or 16 nmol/L), and a higher threshold, as in Buckley et al. (<22 ng/mL or 70 nmol/L), good sensitivity was reported for true-positive ectopic pregnancies, at 88% and 100%, respectively. However, specificity was poor, with false-positive rates of 40% and 27%, respectively, driven by intrauterine pregnancies diagnosed below the same thresholds [39,40]. These findings indicate that low progesterone concentrations may help triage possible ectopic pregnancies but cannot reliably discriminate ectopic from intrauterine pregnancies. Dart et al. studied 160 patients in whom transvaginal ultrasound was indeterminate, including non-specific fluid collections, strengthening a potential triage role for progesterone in abnormal and potentially ectopic pregnancies. These observations were also supported by an earlier meta-analysis by Mol et al. of 26 studies, which identified only 0.3% of 1300 women with progesterone levels less than 5 ng/mL (16 nmol/L) had an intrauterine pregnancy [41]. In that meta-analysis, cohort studies using progesterone threshold values of up to 5–40 ng/mL (16–127 nmol/L) to distinguish pregnancy failure from viable intrauterine pregnancy showed high sensitivity, indicating good performance for identifying non-viability. However, in cohort studies aiming to distinguish ectopic from non-ectopic pregnancy, serum progesterone performed poorly as a diagnostic marker for TEP, with a sensitivity of 15%. A more recent meta-analysis by Verhaegen et al. in 2012, which examined women with pain or bleeding in early pregnancy with an inconclusive ultrasound, also demonstrated good performance for progesterone to predict non-viable pregnancies [21]. Using a cut-off of 3.2–6 ng/mL (10.2–19 nmol/L), pregnancies below this cut-off have a 99.2% probability of being non-viable; however, progesterone again demonstrated poor accuracy for ruling in or out ectopic pregnancy, with a sensitivity of 36.5% and specificity of 41.7% [21].

5.1.3. Prediction of Successful Expectant Management

Evidence supporting progesterone as a predictor of successful expectant management of TEP remains limited. Most of the evidence for the clinical use of progesterone as a prognostic marker for TEP management outcomes relates to methotrexate-treated TEP [42,43]. Jurkovic et al. conducted a placebo-controlled randomised trial of single-dose methotrexate versus expectant management in 80 women with a TEP [44]. Success rates were similar in intention-to-treat analysis at 83%, with methotrexate and 76% with placebo, a difference that was not statistically significant. Baseline progesterone was not associated with the outcome on univariate analysis. On multivariate logistic regression, progesterone did not retain covariate significance; this was only seen with hCG. To our knowledge, this remains the only randomised evidence available, and it does not support a role for baseline progesterone measurement in predicting successful expectant management of TEP. Similar findings have been reported in observational studies. Lipscomb et al. studied 350 women treated with methotrexate treatment for TEP and found that serum hCG was the only factor that was

associated with treatment failure [12]. Shulman et al. performed a retrospective study looking at 210 women with a TEP and found progesterone was not predictive of successful expectant management of TEP using multivariable analysis [14]. Instead, the group found that the final hCG measurement prior to discharge and discharge-to-admission hCG ratio were key predictors for spontaneous resolution of TEP. When the discharge hCG was <650 IU/L combined with a dynamic serum hCG fall of at least 50% during hospitalisation, 97% of TEPs successfully resolved [14].

5.1.4. Summary

In summary, current evidence indicates that low progesterone concentrations are strongly associated with pregnancy non-viability and may plausibly identify TEPs more likely to resolve spontaneously. However, progesterone does not provide sufficient sensitivity or specificity as a stand-alone marker to select women with TEP for successful expectant management. Although existing studies support associations between progesterone and pregnancy viability, they do not demonstrate that a single progesterone value can safely guide management decisions in TEP. Progesterone should therefore not be used independently to determine management of a confirmed TEP.

5.2. Does Progesterone Add Prognostic Value to hCG in the Expectant Management of Tubal Ectopic Pregnancy?

Success rates for expectant management in clinically stable women with low or falling hCG and minimal symptoms vary widely, partly because published studies use different selection criteria. The addition of a baseline progesterone measurement, particularly when interpreted alongside hCG trend and sonographic features, may help refine selection. Several small prospective and retrospective studies have evaluated this approach (Table 1).

Table 1. Summary of key studies assessing the use of progesterone in predicting successful expectant management of tubal ectopic pregnancy.

Study	Population/Setting	Analytical Method	Safety Analysis	Key Finding on Progesterone
Elson et al. 2004 [30]	Single-centre, UK; $n = 179$; 107 (60%) expectantly managed	Prospective; classification and regression tree (CART) decision tree (4 levels, 13 terminal nodes)	No cases of tubal rupture or blood transfusion in women with failed expectant management. In the women who failed expectant management, 30 of 32 (16.8%) underwent laparoscopy and 2 of 32 (1.1%) underwent laparotomy.	Initial hCG was the best single predictor. Within the intermediate hCG stratum, progesterone was selected as the next discriminating variable using an initial cut-off of 10 nmol/L and a further downstream split of 50 nmol/L. Maternal age and gestational age also retained.
Mavrelos et al. 2013 [45]	Single-centre, UK; $n = 474$; 256 (54%) expectantly managed	Prospective observational; validated the Elson 2004 decision-tree protocol	No cases of blood transfusion in women who failed expectant management. All women were treated by laparoscopy. In total, 4 of 40 women (0.8%) had evidence of intraperitoneal bleeding.	Validated the Elson protocol which incorporates progesterone. Eliminated medical or surgical treatment in >1/3 of women with TEP.

Table 1. *Cont.*

Study	Population/Setting	Analytical Method	Safety Analysis	Key Finding on Progesterone
Memtsa et al. 2020 [46]	Single-centre, UK; $n = 93$; 51 (55%) expectantly managed	Prospective observational, but pre-selected hCG < 1500 IU/L. Use of multivariable logistic regression.	In total, 2 of 9 (2.2%) women who failed expectant management had evidence of haemoperitoneum.	hCG and progesterone both retained as independent predictors. Progesterone significant only after adjusting for hCG. Other biomarkers (inhibin A, activin A, hsCRP) not predictive.
Shulman et al. 2023 [14]	Single-centre, Israel; $n = 210$	Retrospective observational; multivariable logistic regression	In total, 5 of 37 (2.4%) women who failed expectant management had evidence of haemoperitoneum.	Progesterone was not identified as an independent predictor. Final hCG before discharge and the discharge-to-admission hCG ratio were the independent predictors.
Graham et al. 2026 [31]	Single-centre, UK; $n = 798$ of 1968	CHAID decision tree (updated Elson methodology)	No information provided.	Initial hCG remained the best single predictor. Progesterone was used as a second-tier discriminatory variable at a cut-off of 7 nmol/L in combination with mean ectopic diameter (cut-off 16 mm).

Abbreviations: hCG, human chorionic gonadotrophin; TEP, tubal ectopic pregnancy; CART, classification and regression tree; CHAID, chi-squared automatic interaction detection; hsCRP, high-sensitivity C-reactive protein.

5.2.1. Evidence from Observational Cohort Studies

Elson et al. conducted a prospective observational study of 179 women with TEP managed expectantly and surgically and found both hCG and progesterone levels were lower in the expectantly managed group [30]. Using these thresholds, alongside sonographic morphology and gestational age, the authors developed a classification and regression tree (CART) model to predict the likelihood of successful expectant management [30]. This was subsequently validated prospectively in a cohort of 474 women, of whom 256 (54%) met the selection criteria [45]. More recently, Graham et al. conducted a single-centre retrospective observational cohort study looking at 798 women who chose expectant management of TEP [31]. Of these, 64% successfully completed expectant management and the remainder required intervention [31]. The authors compared morphological and biochemical differences between successful and unsuccessful cases to define parameters useful for a clinical decision tree. Successful expectant management was associated with lower hCG (205 [91–562] vs. 910 [515–1457] IU/L) and progesterone concentrations (9 [5–20] vs. 23 [12–34] nmol/L). Their chi-squared automatic interaction detection (CHAID) decision tree therefore first stratified cases according to initial hCG concentration and then further subdivided using either progesterone concentration (<7.0 nmol/L) or mean ectopic diameter (>16 mm) [31]. Other studies have further explored the approach of a biomarker-guided selection. Memtsa et al. conducted a prospective study looking at 93 women with a confirmed TEP [46]. Fifty-one of 93 cases resolved without intervention (51/93; 55%) [46]. When assessing hCG, progesterone, inhibin A, activin A and high-sensitivity

C-reactive protein (hsCRP), only hCG and progesterone retained statistical significance in multivariable logistic regression models [46]. However, progesterone only became significant after adjusting for hCG, suggesting it may function best as a complementary prognostic marker [46]. Overall, these findings indicate that in appropriately selected individuals, expectant management of TEP can be achieved with a success rate of 60–97%. These studies are summarised in Table 1. A summary of the differences in clinical and diagnostic utility of both hormones is summarised in Table 2.

Table 2. Comparison of hCG and progesterone as clinical and diagnostic markers in TEP.

Attribute	hCG	Progesterone
Source and determinant	Secreted by syncytiotrophoblast in proportion to mass of viable trophoblast.	Secreted by the corpus luteum until the luteoplacental shift, under the influence of hCG.
Form in which marker is interpreted	Interpreted dynamically, as a trend or as a ratio.	Interpreted as a single baseline concentration.
Distinguishing ectopic from non-ectopic pregnancy	Predictive value only present with ultrasound; combined with an adnexal mass it is diagnostic.	Poor sensitivity and specificity on its own.
Identifying non-viability	Limited when used alone.	A value in a 3–6 ng/mL (10–19 nmol/L) range carries a 99.2% probability of non-viability.
Relationship to ectopic size	A single value is not predictive of ectopic size.	No demonstrated correlation.

Abbreviations: hCG, human chorionic gonadotrophin; TEP, tubal ectopic pregnancy.

Two important considerations remain when assessing the above data. First, treatment success rate alone does not establish the safety of expectant management of TEP. Failure may involve worsening symptoms, psychological morbidity, persistent hCG or significant consequences such as tubal rupture and the need for emergency surgery, yet these outcomes are inconsistently reported. Future studies should report these alongside treatment success. Secondly, decision-tree analyses carry important limitations. Neither Elson et al. or Graham et al. reported conventional measures of model discrimination nor compared the performance of these tables with progesterone excluded, making their independent contribution unclear. Derived cut-offs also may also be susceptible to overfitting and therefore require external validation. Finally, neither study describe management of missing data, which may introduce selection bias, especially as progesterone is not often routinely measured.

5.2.2. Future Directions: Integrated Prognostic Models

Beyond a simple cut-off approach, modern statistical methods such as logistic regression, multivariable risk models, and machine learning approaches including gradient-boosted trees offer the prospect of integrating progesterone with hCG, sonographic features and maternal demographic data into a single individualised risk estimate. Such models would mirror the trajectory taken in PUL triage, where multivariable models have outperformed single-biomarker thresholds [20,47,48]. An important next step is to determine whether similar models can be developed and prospectively validated to support personalised management of confirmed TEP.

5.2.3. Summary

In summary, progesterone may add prognostic information beyond hCG alone but its additional value remains incompletely defined. Current evidence shows that within a

stratum defined by initial hCG, progesterone has been selected as a discriminating variable in more than one decision-tree model and may assist in estimating the likelihood of success in expectant management of TEP. However, it is important to note that the role of progesterone is secondary to hCG and accordingly, should not guide treatment in isolation.

5.3. Limitations and Challenges to the Use of Progesterone as a Prognostic Marker for Expectant Management of Tubal Ectopic Pregnancy

Several factors limit the use of progesterone as a prognostic biomarker for expectant management of TEP and should be addressed in future research. First, most published series evaluating progesterone in TEP are single-centre studies with modest sample sizes, limiting statistical power and generalisability. A large multicentre randomised controlled trial (RCT) would provide more robust evidence, but important ethical and methodological barriers challenge such trials. Jurkovic et al. obtained ethical approval for a placebo-controlled randomised trial of methotrexate versus expectant management; however, only 80 women were recruited over approximately nine years at a single high-volume centre [44]. Replicating or exceeding this would probably require international collaboration, particularly as acceptability of expectant management may be constrained by concerns of tubal rupture.

Consequently, current evidence in this area predominates from prospective and retrospective observational studies rather than interventional trials. Any future RCT would need to incorporate established ethical and clinical indicators into the trial protocol, including serial hCG trends, sonographic findings, symptomatology, and haemodynamic status, thus influencing management decisions. These variables are themselves strongly associated with pregnancy outcome and may influence the timing of intervention, making it difficult to isolate the independent predictive value of progesterone. Although these factors are not necessarily confounders in the classical epidemiological sense because randomisation can balance confounding between study groups, they represent competing prognostic factors and potential co-interventions that may attenuate or obscure the additional predictive contribution of progesterone and hCG.

Practical challenges are also substantial. The sample size required to detect a clinically meaningful difference in rare outcomes, such as tubal rupture risk, would probably exceed the capacity of a single centre and would require a coordinated large multicentre study with a standardised consent process and harmonised progesterone assays. Without such standardisation, heterogeneity in recruitment, monitoring thresholds and laboratory methods could reduce the ability of a trial or cohort study to determine the true prognostic utility of progesterone. Assay variability poses a particular challenge. Studies so far report serum progesterone documented by a range of automated immunoassays that differ in specificity and cross-reactivity, which may lead to inter-platform variability. The progesterone thresholds proposed in the literature span 7–70 nmol/L and so may not be directly comparable or generalisable in real-world early pregnancy units. This complicates the adoption of any published threshold and is a further reason for heterogeneity between studies. However, standardisation across labs should make this feasible.

Women conceiving through assisted reproductive techniques and receiving luteal-phase or first-trimester progesterone support require consideration, because serum progesterone concentrations in this context may not reflect endogenous trophoblast activity alone and the biomarker's prognostic value may be substantially altered. Although methods such as liquid chromatography–tandem mass spectrometry may be able to distinguish between endogenous and exogenous progesterone, implementing this as routine in a trial setting would be extremely challenging [49,50]. Further work is needed to determine the impact of exogenous progesterone and other clinical parameters to determine whether they should be included in diagnostic or prognostic algorithms. Only Elson et al. reported

exogenous progesterone use; none of the women received supplementation. Therefore, when exogenous progesterone is not reported, measured progesterone concentrations may not only reflect endogenous luteal and trophoblastic activity, but potentially bias derived thresholds and attenuate observed associations with outcomes.

Future research should also broaden the outcomes measured beyond treatment success alone. Many studies do not consider patient satisfaction, psychological morbidity or mental health outcome measures, yet patient preference is central to the shared-decision making that underpins the management of all TEPs. In many units, eligibility for expectant or medical management depends primarily on clinical stability and the ability to attend follow-up. Beyond these criteria, the factors that commonly influence patient choice in ectopic management include the wish for future fertility (and the impact of methotrexate delaying efforts to conceive, and the impact of salpingectomy or salpingostomy), the balance between avoiding invasive surgery and quick resolution of the pregnancy, and personal and cultural beliefs about one's health. These priorities are reflected in the qualitative study by Wu et al. [51]. A multicentre cohort study that captures these dimensions alongside clinical outcomes would substantially strengthen the case for any updated selection framework.

6. Conclusions

The management of TEP remains a clinically important area in which decisions regarding non-surgical treatment are frequently made in the context of an incomplete evidence base. Although hCG remains the principal biomarker in current practice, it has recognised limitations as a single predictor of clinical course. This limitation is particularly relevant when selecting clinically stable women for expectant management, where accurate prognostic assessment is required to minimise unnecessary intervention while preserving patient safety.

Progesterone is already incorporated into the assessment of PUL and the triage of failing pregnancies, a proportion of which are diagnosed with a TEP. However, current evidence does not support the use of a single progesterone measurement as either a stand-alone discriminator of TEP or an independent predictor of expectant management success. Its potential clinical value is more plausibly balanced within a broader prognostic framework that includes established biochemical, sonographic and clinical parameters.

In this context, progesterone may have a role as an adjunctive biomarker within multivariable prediction models, particularly as a second-tier stratification tool used alongside serial hCG trends, ultrasound findings and symptom assessment within a decision-tree model. Such an approach could refine selection for successful expectant management, but stand-alone progesterone should not currently be used to replace established criteria or clinical judgement.

Progesterone warrants further consideration in this context. It is inexpensive, widely available and already measured in many early pregnancy units. Future research should prioritise adequately powered multicentre prospective cohort studies and randomised controlled trials that account for exogenous progesterone exposure, assay variability, patient choice, psychological morbidity and mental well-being and consistent endpoint definitions. In our view, the development and external validation of multivariable predictive models incorporating progesterone alongside established markers represents an important next step. Until such evidence is available, expectant management should continue to be guided by serial hCG, ultrasound findings, symptomatology and suitability for follow-up, with patient safety and preference remaining pivotal.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/endocrines7040069/s1: Supplementary Table S1: Mixed Methods Appraisal Tool (MMAT) to appraise non-randomised qualitative studies.

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Abbreviations

The following abbreviations are used in this manuscript:

TEP	Tubal ectopic pregnancy
GnRH	Gonadotrophin-releasing hormone
FSH	Follicle-stimulating hormone
LH	Luteinising hormone
hCG	Human chorionic gonadotrophin
PUL	Pregnancy of unknown location
BMI	Body mass index
LPD	Luteal Phase Deficiency
CART	Classification and regression trees
CHAID	Chi-squared automatic interaction detection
RCT	Randomised controlled trial
hsCRP	High-sensitivity C-reactive protein
uNK	Uterine natural killer cells

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