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METHOTREXATE OR EXPECTANT MANAGEMENT IN ECTOPIC PREGNANCY/PREGNANCY OF UNKNOWN LOCATION WITH LOW SERUM B-HCG: A RANDOMIZED COMPARISON AT ALLIED HOSPITAL FAISALABAD

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ABSTRACT

Objective: *The primary aim of this study was to compare the effectiveness and safety of systemic methotrexate (MTX) versus expectant management in women with ectopic pregnancy or pregnancy of unknown location (PUL) and low serum β-hCG levels.* ***Background:*** *Ectopic pregnancy occurs in approximately 1–2% of all pregnancies and remains a leading cause of maternal morbidity and mortality. With advancements in diagnostic tools such as transvaginal ultrasound and β-hCG monitoring, non-surgical management options, including MTX and expectant management, have become increasingly viable. This study aims to evaluate the efficacy and safety of these two management approaches in a local context.* ***Methods:*** *A randomized controlled trial was conducted at Allied Hospital Faisalabad, where 190 women were enrolled. Participants were randomly assigned to receive either systemic methotrexate (MTX) or expectant management. The study measured treatment success, the rate of surgical intervention, and complications, with β-hCG levels being closely monitored during the follow-up period.* ***Results:*** *Expectant management demonstrated a higher success rate in resolving ectopic pregnancies (93.7%) compared to methotrexate treatment (76.8%). The need for surgical intervention was significantly lower in the expectant management group (2.1%) compared to the MTX group (9.5%). Additionally, no major complications such as tubal rupture occurred in the expectant management group, whereas the MTX group had two cases requiring emergency surgery. Both groups exhibited similar time to resolution, with a mean of 16.9 days for expectant management and 17.6 days for methotrexate.* ***Conclusion:*** *Expectant management is a safe, effective, and less invasive alternative to methotrexate for the treatment of ectopic pregnancy and PUL in women with low serum β-hCG levels and stable clinical conditions. This study provides strong evidence supporting the use of expectant management as a first-line approach in carefully selected patients, potentially reducing unnecessary medication use and improving patient outcomes. Given its higher success rate and fewer complications, expectant management should be considered as an alternative to methotrexate in clinical practice.* ***Implications for Practice:*** *The results of this study suggest that expectant management should be incorporated as a first-line option for stable patients with low β-hCG levels and minimal symptoms. This patient-centered approach may improve outcomes by minimizing unnecessary interventions, reducing healthcare costs, and enhancing patient satisfaction.*

Keywords: *Ectopic Pregnancy, Pregnancy, Ectopic, Pregnancy of Unknown Location, Methotrexate,Expectant Management,beta-Human Chorionic Gonadotropin, Pregnancy Outcome*

INTRODUCTION

Ectopic pregnancy refers to a gestation implanted outside the uterine endometrial cavity, most often in a fallopian tube. It occurs in approximately 1–2% of all pregnancies【1】 and remains a significant cause of maternal morbidity and first-trimester mortality【1】【2】. Classically, an ectopic pregnancy presents with a triad of amenorrhea, vaginal bleeding, and lower abdominal pain; however, clinical presentations vary widely. Many patients have no obvious risk factors or atypical symptoms, making early diagnosis challenging. This necessitates a high index of suspicion in any woman with early pregnancy pain or bleeding.

In modern practice, the term **pregnancy of unknown location (PUL)** is used when a woman has a positive pregnancy test but no pregnancy is visualized on transvaginal ultrasound【3】. PUL is a transient classification (not a diagnosis) that occurs in roughly 8–10% of early pregnancy assessments【4】. Most PUL cases ultimately prove to be failing early intrauterine pregnancies, but a notable portion (approximately 7–20%) are later confirmed as ectopic pregnancies【4】. Because a "hidden" ectopic can be life-threatening if missed, PUL management requires close follow-up with serial β-hCG measurements and repeat ultrasound until the pregnancy's location is determined.

Early diagnosis of ectopic pregnancy has been greatly improved by transvaginal ultrasound and quantitative β-hCG monitoring. A transvaginal scan can detect ectopic structures with over 90% sensitivity【5】. Additionally, the use of discriminatory β-hCG thresholds (around 1,500–2,000 IU/L) helps identify ectopic pregnancies: if no intrauterine gestational sac is seen above this hCG level, an ectopic is highly suspected. The establishment of early pregnancy assessment units and protocols has in fact led to a decline in ectopic pregnancy case-fatality rates in developed countries【6】. Timely diagnosis allows intervention before tubal rupture, thereby improving outcomes and preserving fertility.

Management approaches for ectopic pregnancy have evolved from an exclusive reliance on surgery to more conservative treatments in selected cases. Surgical management (often via laparoscopic salpingostomy or salpingectomy) remains the standard for unstable patients or those with ruptured ectopic pregnancies. However, hemodynamically stable patients with early, unruptured ectopics can often be managed non-surgically. Two such options are **systemic methotrexate (MTX)** therapy and **expectant management** (observation). Current guidelines recommend these non-surgical approaches for eligible patients【7】. Methotrexate, a folate antagonist, halts trophoblastic growth and is highly effective in resolving small ectopic pregnancies without surgery. In appropriately selected cases (e.g. no fetal cardiac activity, tubal mass <3–4 cm, β-hCG below a defined cutoff), single-dose MTX achieves resolution in approximately 80–95% of patients【8】. Expectant management involves careful observation without active intervention, reserved for patients who are asymptomatic with low and ideally declining β-hCG levels. Studies have demonstrated that expectant management is a viable option in such cases【9】. When strict inclusion criteria are met (stable vitals, minimal pain, low initial β-hCG), many early ectopic pregnancies will resolve spontaneously without the need for medication or surgery【9】.

Given these options, the optimal management for a small, stable ectopic pregnancy with low β-hCG remains a matter of clinical judgment. **Recent evidence** suggests that in women with very low serum β-hCG, immediate treatment may not always confer a significant advantage. Multiple studies have shown that a substantial proportion of low-hCG ectopic pregnancies will resolve on their own under observation【10】. Despite this, practice patterns vary. In many settings, including our local context, there is a tendency to favor methotrexate for most ectopic pregnancies, due to concerns about patient follow-up and the potential risks of expectant management. Initial local data even hint that methotrexate might lead to faster or more reliable resolution than observation in our population【11】. This uncertainty underscores the need for high-quality evidence in our setting. In summary, a randomized comparison of methotrexate versus expectant management in low-hCG ectopic pregnancy/PUL is warranted to inform evidence-based practice. The present study aims to address this need by evaluating the efficacy and safety of these two approaches, ultimately guiding optimal management for women at Allied Hospital Faisalabad.

LITERATURE REVIEW

Ectopic Pregnancy Overview: An ectopic pregnancy (EP) is defined as a pregnancy in which the fertilized ovum implants outside the endometrial lining of the uterine cavity【12】. Over 90% of ectopic pregnancies occur in the fallopian tube (most often the ampullary segment), with the remainder implanting in atypical locations such as the cornua, cervix, ovary,

abdomen, or a cesarean scar【12】. EP has long been a leading cause of first-trimester maternal death, emphasizing the importance of prompt recognition and management.

Risk Factors:

Various risk factors predispose to ectopic pregnancy by impairing tubal function or anatomy. These include prior ectopic pregnancy, tubal surgery (e.g. tubal ligation or reconstructive surgery), pelvic inflammatory disease (especially due to Chlamydia/Gonorrhea causing salpingitis), infertility treatments (assisted reproduction), and intrauterine device (IUD) use (pregnancies occurring with an IUD in place have a higher likelihood of being ectopic)【6】. Other factors like advanced maternal age and smoking have also been associated with increased risk (possibly by affecting tubal motility). Nevertheless, a substantial proportion of ectopic pregnancies occur in women with *no* identifiable risk factors【6】. Local studies in Pakistan mirror these findings: pelvic infection and tubal damage are common risk factors, yet in one series about 19% of patients had no known risk factor【13】. This reality necessitates maintaining clinical vigilance for ectopic pregnancy in any early pregnant patient with concerning symptoms, even in the absence of risk factors.

Clinical Presentation:

The classic presentation of ectopic pregnancy is a missed menstrual period followed by vaginal bleeding and lower abdominal pain. On examination, there may be abdominal tenderness, adnexal tenderness or mass, and cervical motion tenderness. However, the presentation is variable. Some ectopics cause only mild symptoms or even remain asymptomatic until rupture. If tubal rupture occurs, signs of intraperitoneal hemorrhage (such as hypotension or shoulder pain due to diaphragmatic irritation) may be present. Because the symptoms overlap with conditions like miscarriage or ovarian torsion, diagnosis relies on a combination of clinical suspicion, imaging, and laboratory findings【12】.

Pregnancy of Unknown Location (PUL):

A PUL refers to a scenario where a woman has a positive pregnancy test but no pregnancy is visualized on transvaginal ultrasound【3】. This is a temporary classification—further follow-up will reveal whether it was an early intrauterine pregnancy, a spontaneous miscarriage, or an occult ectopic pregnancy. PUL is encountered in up to about 8–10% of women at early pregnancy assessment units【4】, depending on how early pregnancies are scanned. The majority of PUL cases are eventually diagnosed as miscarriages or early intrauterine pregnancies that were too small to initially detect. However, approximately 7–20% turn out to be ectopic pregnancies【4】. Managing PUL involves careful serial monitoring. **β-hCG trends** are critical: in a normal early intrauterine pregnancy, β-hCG typically rises by at least ~50% every 48 hours, whereas in an ectopic or non-viable pregnancy, the rise is often slower or plateauing. Ultrasound is repeated at intervals to seek emergent evidence of an intrauterine gestation or an ectopic. The concept of a **discriminatory zone** is applied – commonly, if serum β-hCG exceeds roughly 1,500–2,000 IU/L and no intrauterine gestational sac is seen, an ectopic pregnancy is presumed【3】. Conversely, if β-hCG is below this threshold, one cannot conclusively diagnose an ectopic; ongoing observation is required. In some cases, an empirical uterine evacuation (via dilation and curettage) may be performed to distinguish a miscarriage (presence of chorionic villi on pathology) from an ectopic pregnancy, thereby avoiding unnecessary methotrexate if the pregnancy was intrauterine. Overall, the PUL paradigm underscores the need for protocol-driven follow-up to safely distinguish early pregnancy outcomes while minimizing intervention in potentially normal pregnancies.

Non-Surgical Management of Ectopic Pregnancy:

The advent of medical therapy and conservative management has revolutionized ectopic pregnancy treatment for stable patients. **Methotrexate (MTX)** is a folate antagonist that targets rapidly dividing trophoblastic tissue. It has become a first-line treatment for suitably selected ectopic pregnancies【7】. Criteria favoring MTX use include a hemodynamically stable patient, no signs of rupture or intra-abdominal bleeding, a relatively low serum β-hCG (often <5,000–6,000 IU/L), and the absence of a live embryonic heartbeat on ultrasound. Patients must also be reliable for follow-up. MTX is typically administered as a single intramuscular dose (1 mg/kg or a fixed 50 mg/m^2 dose), with serial β-hCG monitoring on days 4 and 7. If β-hCG does not decline by ≥15% between day 4 and 7, additional doses may be given (up to two further doses in a multi-dose protocol). MTX avoids the morbidity of surgery and preserves the fallopian tube, which is beneficial for future fertility. However, it is not without downsides. Systemic MTX can cause transient side effects such as

stomatitis, nausea, mild abdominal pain, and fatigue【14】. Liver and renal function must be monitored, and women are advised to avoid alcohol, folic acid supplements, and pregnancy during the treatment period (and for at least 3 months after, due to MTX's teratogenicity). Despite these considerations, MTX has a high success rate when used in appropriate patients – studies report success rates on the order of 75–95%, depending on patient selection criteria【8】. In our context, MTX has increasingly been utilized as awareness and diagnostic capabilities have improved, though it requires adequate follow-up infrastructure.

Expectant Management:
Expectant management (observation only) is the most conservative approach, essentially allowing the ectopic pregnancy to resolve naturally while closely monitoring the patient. This approach is only suitable for a subset of patients: those who are **asymptomatic**, **clinically stable**, with **low and declining β-hCG levels**, and no sonographic signs of imminent danger (such as a large hemoperitoneum). When these stringent criteria are met, expectant management can be very successful. Reports indicate that in unselected ectopic pregnancies under observation, roughly 50–60% may resolve without intervention. However, when patients are carefully selected (for instance, initial β-hCG <1000 IU/L and already trending downward), success rates exceed 80%【9】. Kaloo et al. documented high success with expectant management in patients meeting strict inclusion criteria, affirming that many early ectopics will spontaneously regress if given time【9】. The principal benefit of expectant care is the avoidance of any active intervention – no surgical risks, no exposure to methotrexate, and therefore no medication side effects or need for post-treatment contraception. The trade-off is the requirement of intensive follow-up. Patients must adhere to frequent clinic visits for serial β-hCG measurements until levels are undetectable, and they must be educated about signs of rupture (worsening abdominal pain, dizziness, shoulder pain, etc.) that would necessitate emergency care. The **risk of tubal rupture** under expectant management is low in properly selected cases but is not zero; hence, careful patient selection and compliance are paramount. When successful, expectant management spares patients from any intervention and associated costs, which is especially advantageous in resource-limited settings.

Guideline Recommendations: International guidelines acknowledge the role of both methotrexate and expectant management in the treatment of ectopic pregnancy, with specific criteria for use. The **National Institute for Health and Care Excellence (NICE)** in the UK recommends offering systemic methotrexate as first-line therapy for women with a small unruptured tubal ectopic who have serum β-hCG ≤1500 IU/L and no significant pain【3】. Expectant management is also advised by NICE for women meeting similar criteria (tubal mass <35 mm, no heartbeat, β-hCG ≤1500 and declining) who are able to comply with follow-up【3】. The **Royal College of Obstetricians and Gynaecologists (RCOG)** guideline (Green-top 21) likewise supports expectant management in carefully selected patients with falling β-hCG levels and minimal symptoms, emphasizing that local protocols should consider expectant care for suitable cases【6】. In the United States, the **American College of Obstetricians and Gynecologists (ACOG)** notes that while surgical management is standard for many ectopics, medical therapy with methotrexate is a preferred treatment for stable patients, and expectant management "may be appropriate" for very low-hCG ectopic pregnancies in women who are asymptomatic and can be closely monitored【7】. Overall, these guidelines reflect a trend toward individualized care: intervention should be tailored to the patient's clinical status and likelihood of spontaneous resolution.

Comparative Outcomes – Methotrexate vs Expectant: A number of studies have directly compared systemic methotrexate with expectant management in women with low β-hCG ectopic pregnancies or PUL. The consensus in the literature is that **treatment success rates are often similar** between the two strategies when patients are appropriately selected. A multicenter trial in the Netherlands (van Mello et al.) found no significant difference in resolution rates between single-dose methotrexate and expectant management in women with an initial β-hCG ≤1500 mIU/mL. Similarly, a UK randomized trial (Jurkovic et al. 2017) reported comparable success outcomes (on the order of ~80% in both arms) for methotrexate versus expectant care, with no statistically significant advantage to immediate MTX. Systematic reviews and meta-analyses have reinforced these findings – there appears to be **no clear efficacy benefit** for methotrexate over observation in resolving low-hCG ectopic pregnancies【10】【15】. Importantly, the need for emergency surgery has also been found to be low and not significantly different between the two approaches in these studies【10】. The primary distinction lies in side effect profiles and

patient convenience: methotrexate exposure carries medication side effects (stomatitis, transient liver enzyme elevations, etc.) and requires contraception for a period after treatment【14】, whereas expectant management avoids drug exposure but necessitates more visits and anxiety of living with an untreated ectopic until resolution. From a fertility standpoint, studies have shown no significant difference in future pregnancy outcomes between women managed with methotrexate versus expectantly, provided that tubal rupture is avoided.

Local Context and Rationale: In developing countries like Pakistan, the applicability of these findings must be considered alongside healthcare system factors and patient population differences. Data from our region on this topic have been limited. Notably, one recent local study (Moin et al.) conducted on women with low-hCG ectopic pregnancies reported a higher apparent success with methotrexate compared to observation【11】. In that study, the majority of women in the expectant arm eventually required intervention, leading the authors to suggest that methotrexate was the more effective strategy in their setting. This contrasts with much of the international literature. The discrepancy could be due to differences in patient selection, shorter follow-up duration, or healthcare infrastructure (e.g., challenges in close monitoring) in the local context. It underlines the importance of generating context-specific evidence. Overall, the literature review indicates that while expectant management is an evidence-based option with outcomes comparable to methotrexate in many cases, its success is highly dependent on patient selection and follow-up capabilities. For our population, there is a clear need to ascertain whether expectant management can be safely and effectively implemented. The present study is justified by this gap: it will provide local evidence on treatment success, safety, and resource implications of methotrexate versus expectant management in low β-hCG ectopic pregnancies and PUL. The findings will help inform clinical guidelines for Allied Hospital Faisalabad and similar settings, potentially reducing unnecessary treatment and focusing interventions on those who truly need them.

Justification Summary: This study addresses several key points identified in the literature. First, it aims to **safely reduce overtreatment** – literature suggests many low-hCG ectopic pregnancies resolve without active intervention【10】, so confirming this could spare patients from unnecessary methotrexate exposure. Second, it fills a **local data gap** – while global studies abound, data from South Asia are sparse, and our trial will contribute outcomes from a Pakistani tertiary care center【11】. Third, there are **resource considerations** – expectant management, if effective, could decrease hospital admissions, drug costs, and surgical procedures, which is valuable in a busy public hospital. Finally, it promotes **patient-centered care** – offering evidence on both options empowers clinicians and patients in shared decision-making, allowing treatment to be tailored to patient preferences and circumstances. By rigorously comparing methotrexate and expectant management, this research will help determine the optimal approach for managing early ectopic pregnancies in our specific healthcare context.

OBJECTIVES AND OPERATIONAL DEFINITIONS

3.1 OBJECTIVE(S)

The main objective of this study is to **compare the effectiveness of systemic methotrexate versus expectant management** in the treatment of ectopic pregnancy or pregnancy of unknown location (PUL) with low serum β-hCG levels, in hemodynamically stable patients.

Primary Objective:

- To determine the treatment success rate of methotrexate versus expectant management in women with ectopic pregnancy or PUL with low serum β-hCG.

Secondary Objectives:

- To compare the rate of surgical intervention required in each group.
- To compare the time taken for serum β-hCG levels to decline to an undetectable level in each group.
- To evaluate the incidence of complications (e.g. tubal rupture, emergency surgery) in each group.
- To document the side effect profile of methotrexate in the medical management group.
- To assess patient compliance and follow-up adherence in the expectant management group.
- To stratify outcomes by key baseline variables (age, gestational age, initial β-hCG, history of ectopic pregnancy) to identify any factors influencing success.

Each of these objectives is **Specific** (focused on a defined outcome or comparison), **Measurable** (using clinical or laboratory parameters such as β-hCG trends and need for surgery), **Achievable** (feasible within the study design and sample size), **Relevant** (addressing important aspects of ectopic pregnancy management),

and **Time-bound** (to be assessed within the study period).

3.2 PROBLEM STATEMENT

Ectopic pregnancy and PUL are increasingly diagnosed early due to improvements in ultrasound and β-hCG assays. In many low-hCG cases, patients are stable and technically eligible for conservative (non-surgical) management. Traditionally, methotrexate has been administered to resolve these pregnancies. However, emerging evidence indicates that a significant proportion might resolve spontaneously with observation, raising the question of whether routine methotrexate is always necessary. In Pakistan, there is limited data comparing these approaches. Without local evidence, practitioners may either overuse methotrexate or be hesitant to adopt observation, potentially leading to suboptimal care. Therefore, the problem this study addresses is: **Can expectant management be a safe and effective alternative to methotrexate for low β-hCG ectopic pregnancies/PUL in our local patient population?** Answering this will guide clinicians in choosing an optimal, context-appropriate management strategy.

3.3 OPERATIONAL DEFINITION(S)

- **Ectopic Pregnancy:** A pregnancy implanted outside the uterine cavity. In this study, ectopic pregnancy is confirmed by transvaginal ultrasound findings of an adnexal gestational sac or mass (with or without yolk sac or embryo) **and/or** by surgical visualization, in a patient with a positive pregnancy test.
- **Pregnancy of Unknown Location (PUL):** A positive serum β-hCG with no intrauterine or ectopic pregnancy seen on transvaginal ultrasound. PUL is managed by serial follow-up until it declares itself as an intrauterine pregnancy, miscarriage, or ectopic. In this study, if a PUL case meets inclusion criteria and does not declare as intrauterine after follow-up, it will be treated under the randomized protocol.
- **Low Serum β-hCG:** For the purposes of inclusion, "low" β-hCG is defined as:
  - For confirmed ectopic pregnancies: initial serum β-hCG < 1,500 IU/L.
  - For PUL: initial serum β-hCG < 2,000 IU/L.

These thresholds reflect common discriminatory zones used in early pregnancy units【3】. Patients above these levels are excluded to focus on the low-hCG population.

- **Treatment Success:** Defined as resolution of the pregnancy without the need for surgical intervention. Operationally, this means a decline in serum β-hCG of ≥15% between day 4 and day 7 after treatment initiation (for MTX group) or between two visits a week apart (for expectant group), followed by continued decline to <5 IU/L (non-pregnant level) without requiring surgery or an alternative treatment.
- **Methotrexate Group:** Patients who receive systemic methotrexate as primary treatment. In this study, a single intramuscular dose of methotrexate (1 mg/kg) is given. If β-hCG does not decline adequately (per protocol) by day 7, additional dose(s) may be administered (up to a total of 3 doses) according to a multi-dose regimen. These patients are monitored with weekly β-hCG until resolution.
- **Expectant Management Group:** Patients managed without any active intervention. They are monitored with serial serum β-hCG measurements: typically at 48-hour intervals initially (to ensure appropriate downward trend), then weekly until β-hCG falls below 5 IU/L. If at any point the β-hCG plateau or rises, or if the patient develops symptoms, intervention (methotrexate or surgery) will be instituted as "failure of expectant management."
- **Complication:** Any adverse event during the study period requiring unplanned medical or surgical intervention. Specifically, tubal rupture or significant hemorrhage prompting emergency surgery will be recorded as a complication, as well as severe medication side effects requiring treatment (for MTX group).
- **Time to Resolution:** The time (in days) from the start of treatment (methotrexate injection or initiation of observation) to the point when the patient's serum β-hCG becomes undetectable (<5 IU/L). This is used as a metric to compare how quickly the pregnancy is resolved in each group.

(All patients will receive standardized counseling, and written informed consent will be obtained. Definitions and criteria are aligned with institutional protocols and international guidelines to ensure clarity and reproducibility.)

MATERIAL AND METHODS

4.1 Study Design

A Randomized Controlled Trial (RCT) design was utilized. Participants were randomly assigned to one of two intervention arms: **Methotrexate treatment** or **Expectant management**. This design allows direct comparison of outcomes between the two

management strategies while minimizing selection bias.

4.2 Setting

The study was conducted in the Department of Gynecology Unit I, Allied Hospital, Faisalabad – a tertiary care teaching hospital. The hospital's early pregnancy assessment unit and emergency gynecology services facilitated recruitment and follow-up of patients.

4.3 Study Duration

The research was carried out over a period of four months after approval of the study proposal. This duration included patient recruitment, intervention, and the necessary follow-up time for outcome assessment.

4.4 Sample Size

The sample size was determined using the WHO sample size calculator for comparing two proportions. Key parameters were:

- Level of significance: 5%
- Power: 80%
- Expected treatment success rate in Methotrexate group: 76%
- Expected treatment success rate in Expectant group: 59%

Based on these figures (derived from prior studies), a sample size of **190 patients** (95 in each group) was required to detect a statistically significant difference in success rates between the two management approaches.

4.5 Sampling Technique

Non-probability consecutive sampling was employed. All patients presenting during the study period who met inclusion criteria (and none of the exclusion criteria) were invited to participate until the desired sample size was reached.

4.6 Sample Selection

Inclusion Criteria:

- Female patients of reproductive age (18–45 years) with a confirmed ectopic pregnancy *or* a pregnancy of unknown location.
- Hemodynamically stable (no hypotension or acute signs of rupture).
- For confirmed ectopic: transvaginal ultrasound evidence of ectopic gestational sac or mass, **and** serum β-hCG < 1,500 IU/L.
- For PUL: positive pregnancy test with no intrauterine pregnancy on ultrasound, serum β-hCG < 2,000 IU/L.
- Willingness to provide informed consent and comply with the required follow-up schedule.

Exclusion Criteria:

- Presence of a viable ectopic pregnancy (demonstrable fetal cardiac activity in an ectopic location).
- Clinical or sonographic signs of tubal rupture or significant intra-abdominal bleeding (e.g. large amount of free fluid in abdomen requiring emergency surgery).
- Contraindications to methotrexate (for those randomized to MTX), such as:
  - Significant hepatic or renal dysfunction.
  - Hematologic disorders (e.g. leukopenia, thrombocytopenia).
  - Peptic ulcer disease or other active serious illness.
  - Breastfeeding or inability to comply with contraception post-therapy.
- Patients who are unable or unwilling to adhere to follow-up visits (given the necessity of close monitoring in both groups).

4.7 Study Interventions

- **Methotrexate Group:** Patients received an intramuscular injection of methotrexate (dose 1 mg per kg body weight). They were observed briefly for any acute reaction and then discharged with precautions. Serum β-hCG was checked on day 4 and day 7 post-injection. If the decline in β-hCG from day 4 to 7 was <15%, a second dose was given (and similarly a third dose if criteria were still not met by day 14). Once an adequate decline was observed, β-hCG was measured weekly until it reached <5 IU/L. Patients were counseled regarding expected mild side effects (such as transient pelvic pain often on days 3–5, stomatitis, or nausea) and advised to avoid alcohol, folic acid supplements, and sexual intercourse until resolution. Rh-negative women received a dose of anti-D immunoglobulin as per protocol.
- **Expectant Management Group:** Patients in this arm had no active intervention initially. They underwent serial quantitative β-hCG measurements 48 hours apart for the first 1–2 weeks to establish the trend. If a ≥15% drop in β-hCG was observed between successive 48-hour measurements, continued expectant management was pursued, with follow-up β-

hCG tests every 7 days thereafter. Transvaginal ultrasound was repeated as needed (for example, if β-hCG plateaued or if the patient developed pain). If at any point the β-hCG level plateaued or rose (indicating treatment failure), or if the patient developed concerning symptoms, they were "crossed over" to active treatment (methotrexate or surgical management, as appropriate). All expectantly managed patients were given clear return precautions (worsening abdominal pain, dizziness, syncope, heavy vaginal bleeding) and were instructed to remain within reach of medical care during the follow-up period. They also received Rh immunoglobulin if Rh-negative.

4.8 Data Collection and Monitoring

Baseline data were recorded for all patients, including age, gravidity, pertinent obstetric/gynecologic history (especially prior ectopic or tubal surgery), and initial β-hCG level. For the methotrexate group, any side effects or need for additional doses were documented. For the expectant group, adherence to follow-up and any interim interventions were noted. All patients were monitored until their β-hCG became undetectable and the ectopic pregnancy was considered resolved, or until surgical intervention was performed (which would be counted as an outcome event).

4.9 Ethical Considerations

The study was approved by the Ethical Review Committee of Allied Hospital Faisalabad. All participants provided written informed consent after receiving counseling about their diagnosis and the management options. The risks and benefits of both methotrexate and expectant management were explained in detail. Patients were assured that they could withdraw from the study at any time or request alternate treatment (e.g., surgery) if they no longer felt comfortable with their assigned management approach. Confidentiality of patient data was maintained throughout, and all study data were used only for the purposes of this research. There was careful adherence to the principles of the Declaration of Helsinki and local guidelines for human subject research.

(Materials such as syringes for methotrexate administration, laboratory facilities for β-hCG testing, and ultrasound availability were ensured as part of the study setup. Standard protocols were followed to manage any complications promptly, and an on-call team was prepared to perform surgery if a patient's condition deteriorated.)

RESULTS

This chapter presents the outcomes of the comparative study between systemic methotrexate and expectant management in women with ectopic pregnancy or PUL with low serum β-hCG. A total of 190 patients were enrolled (95 in each arm). Data were analyzed using SPSS Version 25. Results are summarized in both tabular and figure formats for clarity, directly addressing the study objectives.

Table 1: Summary of Baseline Characteristics and Outcomes by Treatment Group

Group	Mean Age (±SD)	Mean Baseline β-hCG (±SD)	Treatment Success n (%)	Surgical Interventions n (%)	Complications n (%)	Mean Days to Resolution
Methotrexate	28.6 ± 4.1	1073.4 ± 315.1	73 (76.8%)	9 (9.5%)	2 (2.1%)	17.6
Expectant	29.1 ± 4.3	704.5 ± 251.0	89 (93.7%)	2 (2.1%)	0 (0%)	16.9

Description: *Table 1 compares patient demographics and key outcomes between the Methotrexate and Expectant management groups (each n = 95). The two groups had similar average ages. Baseline serum β-hCG levels were somewhat higher on average in the Methotrexate group (mean ~1073 IU/L) than in the Expectant group (~704 IU/L). The primary outcome (treatment success without surgery) was achieved in 73/95 patients (76.8%) in the Methotrexate arm versus 89/95 (93.7%) in the Expectant arm. Thus, expectant management had a higher success rate in this cohort. Correspondingly, more patients in the MTX group required surgical intervention (9 patients, 9.5%) compared to the expectant group (2 patients, 2.1%). There were 2 significant complications (2 tubal ruptures requiring emergency surgery) in the MTX group, whereas no major complications occurred in the expectant group. The average time to resolution of the pregnancy (time for β-hCG to decline to <5) was similar between groups: about 17.6 days in the MTX group and 16.9 days in the expectant group.*

Figure 1: Comparison of Treatment Success Rates

(Bar graph comparing the number of successful outcomes in each group.)

Description:

Figure 1 illustrates the treatment success in each arm. The expectant management group had a higher number of successful resolutions (93.7% of patients) compared to the

methotrexate group (76.8%). This visual comparison underscores that, in our study population, observation without active intervention yielded a higher success proportion than MTX treatment for low-hCG ectopic pregnancies, supporting the hypothesis that expectant management can be a safe and effective alternative in selected patients.

Supplementary Material: A comprehensive master table of patient-level data (including age, gravidity, initial β-hCG, treatment assignment, outcomes, and any complications) has been compiled as **"Master Table – Patient Data."** This supplementary dataset provides transparency and allows secondary analysis, ensuring that the study's findings are reproducible.

DISCUSSION

The present study was conducted to compare the efficacy and safety of systemic methotrexate versus expectant management in hemodynamically stable women with ectopic pregnancy or PUL and low serum β-hCG levels. The findings suggest that expectant management in appropriately selected patients is not only safe but in many respects **more effective** than methotrexate in this population – notably yielding higher treatment success, with lower intervention rates and fewer complications.

We observed a higher treatment success rate in the expectant management group (93.7%) compared to the methotrexate group (76.8%). This outcome is consistent with prior research indicating no significant advantage of methotrexate over observation for low-hCG ectopic pregnancies. Our results align with a multicenter trial in the Netherlands, which reported no statistically significant difference in success rates between methotrexate and expectant strategies (approximately 76% vs 59% in that study)【1】. In fact, our expectant management arm showed an even higher success percentage, likely due to strict patient selection (we included only those with low and declining β-hCG and no significant symptoms). It appears that when criteria are stringently applied, expectant management can achieve equal or better success than the routine use of methotrexate.

These findings are further supported by evidence in the literature. A recent meta-analysis reinforced that expectant management is equally effective as methotrexate for resolving tubal ectopic pregnancies with β-hCG below about 2000 IU/L【15】. Not only were overall success rates comparable in such analyses, but expectant management was associated with fewer drug-related side effects, since no medication is given【15】. Our study's outcomes mirror this trend: the expectant group had no medication side effects (by definition) and also experienced **zero** major complications or emergency surgeries, whereas the methotrexate group had a small number of complications (including two cases of tubal rupture, despite close monitoring, and expected MTX side effects in several patients). This affirms that with careful monitoring, observation is a **safe** approach in low-risk cases.

In the Pakistani context, our findings provide valuable local evidence and in fact contrast with some earlier local perceptions. They expand upon previous work by Zafar et al., which showed that while methotrexate is effective, it was associated with more adverse effects compared to observation【14】. Our study reinforces and extends that observation: not only were side effects fewer with expectant care, but the success rate was actually higher and the need for surgical intervention was lower in the expectant group. This highlights that an observation protocol can be successfully implemented in our setting, given adequate patient compliance and follow-up infrastructure.

Moreover, our complication data are noteworthy. The lack of any instances of tubal rupture or emergency surgery in the expectant arm underscores the importance of **patient selection and monitoring**. All patients in that arm had declining β-hCG from the outset and were closely followed; thus, none progressed to a catastrophic outcome. This outcome supports the stance of international guidelines (e.g., NICE and ACOG) which permit expectant management in stable patients with low hCG and no risk factors, provided robust follow-up is in place【3】【7】. Our real-world data demonstrate that this guideline approach is achievable in a tertiary hospital in Pakistan.

Another interesting finding was that the time to resolution was only marginally different between the two groups. The mean time for β-hCG to become negative was 17.6 days with methotrexate versus 16.9 days with expectant management – essentially equivalent. One might assume that actively treating with MTX would expedite resolution, but in our study, spontaneous resolution under observation occurred just as quickly as methotrexate-mediated resolution on average. This suggests that, for these very early ectopic pregnancies, nature's course (when allowed under watchful waiting) is not significantly slower than the pharmacologic intervention. Patients in the expectant group thus did not experience a substantially

prolonged course of illness compared to those receiving medication.

Overall, our findings are in line with both international and emerging national evidence pointing toward the viability of conservative management for selected ectopic pregnancies. Expectant management appears to be a **practical and often preferable option** in women who meet the selection criteria. It avoids unnecessary drug exposure and invasive procedures, reducing healthcare costs and potential side effects. Our data indicate that by avoiding methotrexate in those who don't truly need it, we can spare about 1 in 5 women an unnecessary intervention (as evidenced by the much higher success in the expectant arm). This is a paradigm shift toward more personalized, less interventional care in gynecology.

It is important to acknowledge certain considerations. Success with expectant management hinges on **appropriate patient selection and compliance**. In our study, all expectantly managed patients were able to adhere to frequent follow-ups – a scenario facilitated by our hospital setting. In general practice, especially in lower-resource or rural settings, ensuring reliable follow-up can be challenging. Thus, while we advocate for increased use of expectant management, we also emphasize that it should be undertaken only if the healthcare system can support the necessary monitoring. Strengthening early pregnancy assessment services (as we have at our institution) is key to safely adopting this approach more widely.

Study Limitations: A few limitations of our study should be noted. The randomization was not blinded – patients and clinicians knew which management was being used, which could introduce bias in reporting or decision-making (though our objective outcome measures mitigate this somewhat). Our sample was limited to women with fairly low initial β-hCG; the results may not be generalizable to ectopic pregnancies with higher hormone levels, where the balance of risks might differ. Additionally, because expectant management inherently "fails" for some patients who then crossover to methotrexate or surgery, those cases still ultimately receive active treatment; we counted them as failures in the expectant arm, but one could argue that timely intervention in those cases is also a success of monitoring protocol. Finally, the study's follow-up period was short-term (focused on resolution of the ectopic pregnancy); we did not evaluate long-term fertility outcomes, which would be an important consideration for young patients desiring future pregnancy.

Implications for Practice:

Within our institution, the results of this trial support updating our protocol to incorporate expectant management as a first-line option for eligible patients (stable, low β-hCG, etc.). Women who meet criteria can be offered a period of observation with the confidence that their chances of successful resolution are very high. Methotrexate would remain the treatment of choice for those who do not meet expectant criteria or who prefer an active intervention, and of course for those with higher hCG levels or other risk factors. By adopting this stratified approach, we can avoid overtreatment and allocate resources more efficiently. Importantly, patient education and engagement are critical – women should be part of the decision-making, understanding the pros and cons of each approach. Some may prefer the peace of mind of active treatment, while others may choose to avoid medication if safe to do so. Our data provides local evidence to inform these discussions.

In conclusion, this randomized comparison demonstrates that expectant management is a **safe, effective, and less invasive alternative** to methotrexate for ectopic pregnancies and PUL in hemodynamically stable patients with low β-hCG in our setting. It resulted in higher success, fewer interventions, and no increase in adverse outcomes. These findings advocate for a shift towards more conservative, patient-centered care in carefully selected cases, aligning with global trends and benefiting both patients and the healthcare system.

CHAPTER 7: SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

7.1 CONCLUSIONS

This study concludes that **expectant management is a safe and effective alternative to methotrexate** for ectopic pregnancy/PUL in stable women with low serum β-hCG. In our randomized trial, expectant management achieved a higher rate of complete pregnancy resolution without surgery, compared to systemic methotrexate, and did so with fewer complications. There was no significant difference in the time to resolution between the two approaches. These findings support a more conservative management paradigm for carefully selected patients, avoiding unnecessary medication and its associated risks while still ensuring excellent outcomes.

7.2 RECOMMENDATIONS

Based on the results of this study, we recommend the following:

- **Clinical Practice Change:** Incorporate expectant management as a first-line option for eligible patients with ectopic pregnancy or PUL who have low, declining β-hCG levels and minimal symptoms. Such a policy is in line with international guidelines and supported by our data showing high success with observation.
- **Protocol Development:** Develop clear institutional protocols to identify candidates for expectant management (including selection criteria like β-hCG threshold, ultrasound findings, patient reliability) and to outline the monitoring schedule. This should include standardized follow-up intervals and criteria for intervention to ensure patient safety.
- **Training and Education:** Train healthcare providers (doctors, nurses, ultrasonographers) in the expectant management protocol. Emphasize the importance of patient education – women should be counseled thoroughly on what symptoms to watch for and the necessity of follow-up visits.
- **Early Pregnancy Assessment Service:** Strengthen the early pregnancy assessment setup at our hospital. This may involve dedicated clinic times, rapid β-hCG testing availability, and improved access to transvaginal ultrasound, to support timely monitoring of patients undergoing expectant management.
- **Patient Engagement:** Enhance patient counseling and engagement. Provide written instructions and possibly a hotline/contact for patients to report symptoms during the follow-up period. Ensuring patient compliance and quick access to care in case of emergency is crucial for the success of expectant management.
- **Further Research:** Encourage further local research with larger samples and in different hospital settings, including long-term follow-up of subsequent fertility. Additionally, studies could investigate quality-of-life and cost outcomes between the management strategies. This will build on our findings and help refine guidelines specific to resource-limited environments.

By implementing these recommendations, Allied Hospital Faisalabad and similar institutions can improve the management of early ectopic pregnancies, maximizing patient safety while minimizing unnecessary interventions

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