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Open Access Journal of Gynecology
ISSN: 2474-9230

Replacing Methotrexate with Letrozole in Cases of Early Ectopic Pregnancy as an Innovative Therapy - A Short Communication

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Short Communication
Volume 5 Issue 1
Received Date: September 29, 2020
Published Date: October 23, 2020
DOI: 10.23880/oajg-16000202

Abstract

In cases of early ectopic pregnancy the only medical therapy advocated till now has been single or multiple dose methotrexates with some preconditions. Here the role of an aromatase inhibitor, letrozole is discussed as a novel drug that possibly can be considered for replacement of methotrexate in view of its simplicity of use, cheap, relatively free of side effects associated with methotrexate, not having many contraindications other than the haemodynamic stability, size of mass, ruptured ectopic pregnancy. Currently letrozole is being utilized commonly for the treatment of hormone sensitive breast cancer, besides as a drug for ovulation induction in cases of poly cystic ovarian syndrome (PCOS). Only more randomized controlled trials (RCTs) are needed before one can safely utilize it in routine clinical practice without fear of any haematological side effects of methotrexate.

Keywords: Early Ectopic Pregnancy; Medical Therapy; Methotrexate; Letrozole

Abbreviations: PCOS: Poly Cystic Ovarian Syndrome; RCTs: Randomized Controlled Trials; EP: Ectopic Pregnancy; FA: Folic Acid; LFT: Liver Function Test; BM: Bone Marrow; RFT: Renal Function Tests; AMH: Anti Mullerian Hormone.

Short Communication

Ectopic Pregnancy (EP) is a significant problem influencing 1% of pregnancies, hence a major factor of maternal mortality in 1st trimester [1-3]. Proper therapy at the right time is key for its management. Management might be surgical, medical or expectant [1]. Surgery involving salpingectomy/salpingostomy is needed classically for advanced/ruptured EP, while methotrexate remains the 1st line therapy for early unruptured EP. Methotrexate can be delivered in the form of single or multidose regimens, having a success rate nearing 93% [3].

Advancements in imaging technology and protocols to screen women at risk have led to earlier detection of ectopic pregnancies [4-9]. As more women with ectopic pregnancies present clinically stable without concern for rupture, options for treatment have expanded beyond surgical management to medical management.

Methotrexate represents a folic acid (FA) antagonist which inhibits the enzyme dihydrofolate reductase, responsible for conversion of FA to tetrahydrofolate that is a cofactor required for DNA as well as RNA generation [3]. Via enzyme dihydrofolate reductase inhibition, it leads to downstream inhibition of DNA synthesis and repair as well as in cell replication as well as. methotrexate prevents trophoblast proliferation as well as stimulates abortion. Efficacy of methotrexate is as good as that of salpingostomy for EP without influencing further fertility.

Yet, methotrexate represents a chemotherapeutic agent might cause side effects like nausea, vomiting, conjunctivitis, stomatitis, gastritis, altered liver function test (LFT), bone marrow (BM) suppression, as well as photosensitivity [1,3]. Methotrexate is not advocated for ruptured EP, in case of patient who has unstable haemodynamics, or where beta-HCG amounts>5000 mIU/mL, that is all suggestive of greater advanced EP [3]. Other contraindications are immunodeficiency, anaemia, thrombocytopaenia, pulmonary disease, peptic ulcer, hepatic or renal dysfunction as well as breast feeding [2]. Thus alternate medical therapies are required.

Recently Mitwally, et al. [10], evaluated the utilization of letrozole for the therapy of EP for the first time. Letrozole represents a 3rd generation aromatase inhibitor which suppresses E2 generation [11-13]. Aromatase being an enzyme responsible for E2 generation, which converts androstendione to estrone as well as testosterone (T) as well as E2 [4]. Letrozole is responsible for blockade of this aromatase function, thus avoiding a key step in the estrogen (E2) generation. Further Letrozole gets utilized for therapy of E2 –based breast cancer or postmenopausal women as well as ovulation induction in women with poly cystic ovarian syndrome (PCOS) [11]. In view of progesterone (P) being believed to be more necessary as compared to E2 for both establishment as well as sustainance of pregnancy [1], it is not immediately clear the reason for which letrozole would disturb EP. Mitwally, et al. [10], posited that inhibiting E2 generation, role might have been underestimated, as well as inhibiting this E2 generation, by utilizing letrozole might disrupt normal physiological functions of progesterone(P) required for sustainance of pregnancy.

A nonrandomized trial was fashioned by Mitwally, et al. [10], involving 42 Egyptian women having tubal EP. Women who got enrolled chose their therapy as well as got divided into 3 arms of 14 patients delivered letrozole, methotrexate, or salpingectomy. That in letrozole arm got 5mg /dayx10days, while methotrexate arm got a single intramuscular injection of 50mg/m^2. β-HCG amount were measurement on day of treatment, day 4, 7 as well as 14 days later. An undetectable β-HCG amount pointed to resolution of EP. Haemoglobin (Hb) levels, blood platelet counts, liver function tests(LFT), renal function tests (RFT), as well as AMH, in the form of measure of ovarian reserve as well as fertility got monitored.

As per the outcomes, letrozole was equally efficacious as methotrexate, having a success rate of 86% for both treatment arms. β-HCG amount even seemed to reduce faster for those treated with letrozole as compared to methotrexate, although it was not a statistically significant variation. No change in Hb as well as platelet counts were seen with Letrozole, while methotrexate caused an escalation of LFT as well as reduction in haemoglobin (Hb) levels as well as platelet counts. No influence on anti mullerian hormone (AMH) was associated with Letrozole 3mth following treatment. The outcomes appear promising, though letrozole got compared with single dose methotrexate, that is somewhat lesser effective as compared to multidose regimen [2].

However one should take the outcome cautiously knowing the limitations of this study. A nonrandomized design was utilized with patients choosing their own therapy. It is essential to use randomization for preventing cofounding–by–indication, that takes place with some property have a greater chance of needing one special therapy [5]. Cofounding–by–indication causes noncomparable arms of therapy. Women having less advanced EP might have wanted to use a newer therapy in Mitwally, et al. [3], study, having the knowledge that their chances of getting a complication was low as well as knowing close follow up would be there for them. Still this trying letrozole appears luring knowing the side effects of methotrexate as well as surgery.

It is tough to find if treatment arms were comparable. Women presenting with advanced EP ,having β-human chorionic gonadotropin (HCG) amounts >3000 mIU/mL, or signs of fetal cardiac action have been ruled out, but data regarding haemodynamics stably results, size of ectopic mass as well as the presence of any amount of peritoneal fluid. Women getting therapy with letrozole had lower β-HCG amounts at baseline as compared to those getting methotrexate or salpingectomy. β-HCG amounts on therapy day were only 1065 mIU/mL, in the Letrozole group, that was less than 1415 mIU/mL, in the methotrexate group. Mitwally, et al. [3], took salpingectomy as control but salpingostomy is preferred usually for the lesser advanced cases and might have better suitability. Thus women with early EP might have chosen Letrozole as compared to methotrexate or salpingectomy. The significance of this is that a lot of early EP having lower β-HCG amounts might resolve on their own without any treatment [1]. Hence, it is feasible that certain EP in Letrozole group might have resolved just with expectant therapy [1].

Further compliance with therapy also has to be taken in account. Here Letrozole was administered in Letrozole group for 10days orally. This regimen might be tougher to follow than methotrexate that needed a minimum of just one injection. A randomized controlled trial (RCT) with an intention to treat evaluation would be required for finding if compliance would influence the efficacy of letrozole [14].

Other limitations of this study were the limited sample size as well as statistical power, along with small follow up duration. Despite no influence of Letrozole on ovarian reserve 3mth following treatment, longer follow up would

aid to find if Letrozole is safe for women as well as their future children. Certain researchers have brought up queries regarding the possible teratogenicity of letrozole [11].

Despite all these Mitwally, et al. [10], give an initial report that favours use of Letrozole as an alternative therapy to methotrexate for EP for which they need to be appreciated for their innovative work. Still randomized controlled trials (RCT) are required to find effectiveness as well as safety of letrozole for EP therapy [15].

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