

Methotrexate in the treatment of tubal ectopic pregnancies – *friend or foe?*

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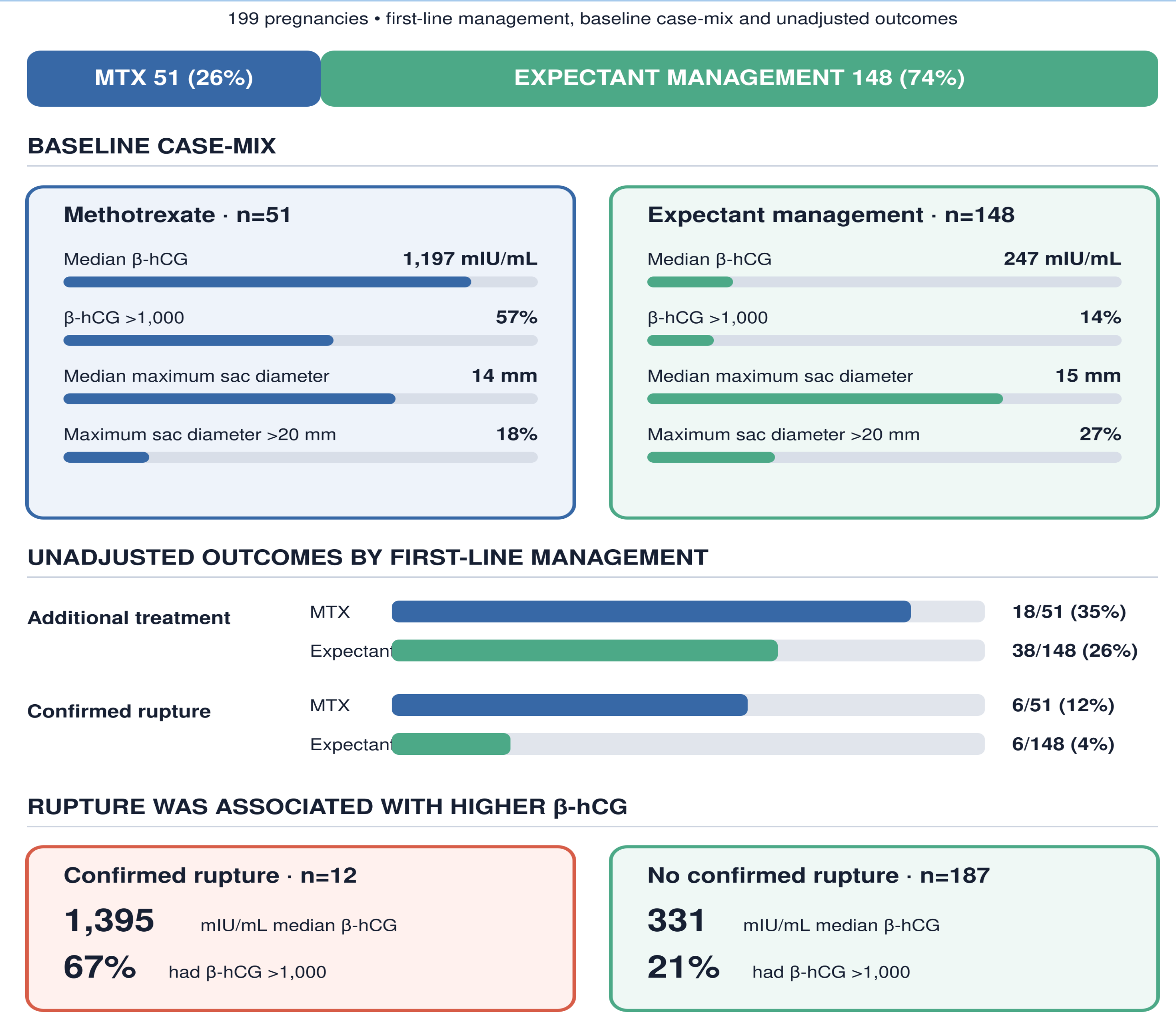
Background:

Methotrexate (MTX) has been used as a non-surgical treatment for ectopic pregnancy for over 40 years and is recommended for appropriately selected, **clinically stable patients**. It is a folate antagonist which inhibits the proliferation of rapidly-dividing trophoblastic cells via inhibition DNA synthesis. Treatment success is strongly influenced by **initial serum β -hCG**, with higher concentrations and evidence of a more developed ectopic pregnancy associated with increased treatment failure. Conversely, recent evidence suggests that expectant management for tubal ectopic pregnancy (TEP) may be **as effective** as methotrexate in stable patients with low β -hCG, while avoiding treatment-related adverse effects. Side effects include abdominal pain, nausea, vomiting, mouth ulcers and light sensitivity, risks of liver injury, and need to wait for 3 months before trying to conceive again, which are understandably **intolerable for many patients**. The optimal selection of patients for medical versus expectant management therefore remains clinically important.

Objective: We aimed to perform a retrospective review of MTX outcomes in a tertiary early pregnancy unit, which has 7-day consultant-led cover, the capacity for close follow up, and serves a population of a wide range of social deprivation levels

Results

Figure 1: A visual summary of the results of our single-centre, retrospective review



Conclusion:

Despite appropriate patient selection and follow-up, MTX use for TEP in our cohort demonstrates **high levels of failure and re-intervention**, and rupture with associated morbidity. This should prompt **reconsideration of the narrow role of MTX in TEP** management, and whether we should proceed directly to surgery in patients with higher β -hCG levels.

Discussion:

Most TEP’s in this cohort were managed expectantly rather than medically, consistent with evidence supporting conservative management in clinically stable patients with low β -hCG. Van Mello et al. found **no significant benefit from single-dose MTX over expectant management in pregnancies with plateauing β -hCG below 1,500 IU/L**, or PUL below 2,000 IU/L. Similarly, the individual participant data meta-analysis by Solangon et al. found **no significant differences in treatment success, surgical intervention or follow-up duration** when β -hCG was below 2,000 IU/L. **Mean time to resolution was only marginally shorter with MTX: 19.7 versus 21.2 days.**

In our cohort, MTX recipients had substantially higher β -hCG but similar sac dimensions, suggesting that **β -hCG was the principal factor influencing treatment selection**. Additional treatment and rupture were more frequent following MTX (however these unadjusted differences should not be interpreted as causal because the MTX group may represent a higher-risk population at baseline). Across the cohort, **rupture was associated with higher median β -hCG and a greater proportion of patients with β -hCG above 1,000 IU/L**.

Treatment selection should not rely on initial β -hCG alone. A recent meta-analysis of 2,804 patients identified fetal cardiac activity, a yolk sac, higher progesterone, greater pre-treatment and day 1–4 β -hCG rises, previous pelvic inflammatory disease and recurrent ectopic pregnancy as predictors of single-dose MTX failure. **Mass size was less consistently predictive.**

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Figure 2: A summary of conclusions from the latest evidence

