# Oral vinorelbine to treat women with ectopic pregnancy: a phase 1 clinical safety and tolerability study

Vinorelbine is a chemotherapy medication used as an oral alternative to other agents (1). Methotrexate is the only medical option available to treat ectopic pregnancy via intramuscular injection (2, 3). It is less invasive than surgery but incurs approximately a 29% risk of requiring rescue surgery (4). An oral therapy to treat ectopic pregnancy does not exist (5). Preclinical studies have identified the potential of vinorelbine as a novel tablet-only treatment for ectopic pregnancies (1). Here, we assessed the safety, toxicity, and tolerability profiles of vinorelbine when administered to women with stable ectopic pregnancies.

## STUDY DESIGN

We performed a phase 1 open-label study. We aimed to recruit 20 women with an ultrasound diagnosis of a tubal ectopic pregnancy. This was a single-site study where women were recruited at North Shore Hospital, Waitemata District Health Board, in New Zealand. Ethical approval was obtained (17/CEN/155), and the trial was prospectively registered (ACTRN12610000684022).

Participants were recruited on the basis of eligibility criteria for methotrexate treatment according to the local institutional protocols. We did not recruit women in whom there was a suspicion of a ruptured ectopic pregnancy (Table 1). Written informed consent was obtained from all participants before treatment.

Each participant was administered an oral dose of 60 mg/m$^2$ of vinorelbine on days 0 and 4. The primary outcome of this study was to assess the safety, toxicity, and tolerability of vinorelbine in patients with stable ectopic pregnancies. Women were assessed clinically (history and examination) and biochemically (full blood count, urea and electrolytes, and liver function tests) on days 0, 4, 7, and 11 and then weekly until the ectopic pregnancy resolved (i.e., human chorionic gonadotropin [hCG] level of $<5$ IU/L).

If the ectopic pregnancy ruptured or active bleeding from the ectopic pregnancy was suspected, prompt surgical management was offered.

The secondary objectives of this study were to determine the effects of vinorelbine on the clinical and biochemical markers of ectopic pregnancy resolution or progression (i.e., treatment failure).

## RESULTS

Ninety-five patients presented with ectopic pregnancy from August 2018 and March 2021 to the Waitemata District Health Board in New Zealand. Of these, 32 were eligible, and 16 were recruited to the trial. Fifteen participants were administered vinorelbine. Patient 15 did not have a decrease in the $\beta$-hCG level with vinorelbine and was taken to theater. Laparoscopy revealed a corpus luteum cyst and retained products of conception. A decision was made to stop recruitment at this point because of the limitations of trial recruitment during the coronavirus disease 2019 pandemic in New Zealand. Thus, 14 participants were included in our study (Fig. 1).

The most common side effects included gastrointestinal upset (n = 7, 50%). Abdominal pain was experienced in 1 participant (n = 1, 7.1%). None of the participants developed neutropenia or liver function derangement.

The mean $\beta$-hCG level on day 0 was 1,117 IU/L, the mean gestational age was 6.79 weeks (standard deviation, $\pm$1.14), and the mean measured size of the adnexal mass was 2.07 cm ($\pm$0.47). After administration of vinorelbine, 78.6% (11/14) of the participants showed a reduction in the serum hCG levels over time (Table 1). Ten (71.4%) of 14 participants had a complete resolution of their ectopic pregnancy without the need for surgery. The median time to resolution was 35 days. Three participants (participants 8, 9, and 12) had a slow decrease in the hCG level over a long period but ultimately achieved a successful outcome (Table 1).

All participants returned to menses within 6 weeks after treatment with vinorelbine. Two participants underwent hysterosalpingography (to determine tubal patency), which revealed normal results. Seven participants had spontaneous intrauterine pregnancies. Five of these pregnancies continued to successful births, those of whom had first trimester miscarriages.

## CONCLUSION

This study demonstrates that vinorelbine is a safe medication with minimal side effects when used to treat stable ectopic pregnancies in women. It had no apparent impact on future fertility of participants. The medical treatment of ectopic pregnancy is less invasive and without surgical risk. In light of these phase 1 data suggesting that the medication is safe, the evaluation of the efficacy of oral vinorelbine to treat ectopic pregnancy in a large randomized controlled trial may be warranted.

**Declaration of interests:** P.C. has nothing to disclose. R.H. has nothing to disclose. T.L. has nothing to disclose. A.M. has nothing to disclose. G.C. has nothing to disclose. A.H. has nothing to disclose. A.A.-A. has nothing to disclose. M.A. has nothing to disclose. B.M. has nothing to disclose. A.H. has nothing to disclose. E.L. has nothing to disclose. P.A. has nothing to disclose. F.B. has nothing to disclose. S.T. has nothing to disclose.

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## TABLE 1

**Values of hCG (IU/L) for each patient at days 0, 4, and 7, percentage decrease in the serum hCG levels between days 0 and 7, outcomes for each patient, and time to resolution (in days).**

| Patient | Day 0 hCG (IU/L) | Day 4 hCG (IU/L) | Day 7 hCG (IU/L) | % decrease from days 0 to 7 | Treatment outcome | Time to resolution (d) |
|---|---|---|---|---|---|---|
| 1 | 898 | 513 | 352 | 61% | Success | 35 |
| 2 | 890 | 370 | 180 | 80% | Success | 35 |
| 3 | 1,150 | 880 | 550 | 52% | Success | 35 |
| 4 | 1,200 | 740 | 87 | 93% | Success | 21 |
| 5 | 806 | 1,911 | 2,528 | (Increase) | Surgery | |
| 6 | 390 | 228 | 155 | 60% | Success | 14 |
| 7 | 574 | 421 | 281 | 51% | Success | 37 |
| 8 | 610 | 632 | 789 | (Increase) | Success | 48 |
| 9 | 936 | 986 | 815 | 13% | Success | 76 |
| 10 | 1,047 | 2,031 | 2,631 | (Increase) | Surgery | |
| 11 | 1,417 | 3,953 | 6,580 | (Increase) | Surgery | |
| 12 | 1,221 | 1,343 | 1,460 | (Increase) | Success | 65 |
| 13 | 2,430 | 3,542 | | NA | Surgery | |
| 14 | 2,805 | 1,847 | 1,479 | 47% | Surgery (rupture) | 35 |

*Note:* hCG = human chorionic gonadotropin.

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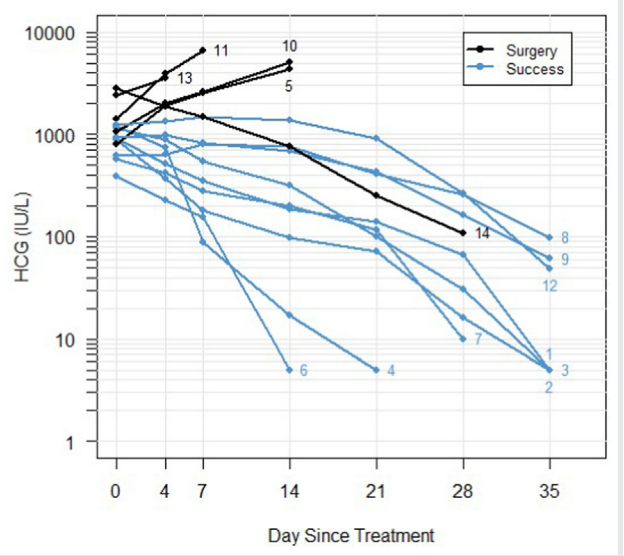
## FIGURE 1




Individual serum human chorionic gonadotropin (hCG) levels in 14 participants administered vinorelbine at day 0, vs. time in days. Participants requiring surgical management are shown by *black lines*; patients treated successfully by vinorelbine are shown by *blue lines*.

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