

To FSH or not to FSH? The addition of mid-follicular FSH does not improve outcomes over standard oral medication protocols

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**Background:** Infertility patients undergoing treatment are often looking for an intermediate step between oral medications/intrauterine insemination (IUI) and in-vitro fertilization (IVF).

**Objective:** We aim to determine if a mid-follicular addition of Injectable gonadotropins to augment a standard oral medication/IUI cycle increases pregnancy rates, with only a modest cost increase.

**Methods:** This is a retrospective cohort study examining five years of data (2017-2021) at one academic-affiliated private practice of patients who underwent oral medications (clomid or letrozole)/IUI (Oral/IUI group) compared to those who did a similar protocol with the addition of 1-2 doses of 150IU FSH between day 8-9 of their cycle (Combo/IUI group). These were both compared to patients who underwent natural cycle donor insemination to serve as a control group (DI group). Primary outcomes were initial positive hcg value, ongoing clinical pregnancy rate as defined as presence of a viable pregnancy at 8 weeks gestation, cycle cancellation rate, and multiple pregnancy rate. Student's t-test and Chi-squared test were used as appropriate.

**Results:** There were a total of 1365 standard oral medication/IUI cycles, 971 Combo/IUI cycles, and 127 TDI cycles. The outcomes are listed in table 1. There was no statistical difference in any of the reproductive parameters between the standard and the combo groups with similar pregnancy, miscarriage, and biochemical pregnancy rates. When comparing the cycles that resulted in clinical pregnancies, there was a significantly higher rate of multiple pregnancies in the combo group (17.2% (11/64) vs. 7.1% (8/112);  $p = 0.04$ ), with one set of higher order multiples (HOM) in the combo/IUI group and two sets in the oral/IUI group. However, the overall multiple pregnancy rate of all cycles was low (19/2336, 0.8%) with no difference between groups (1.1% vs. 0.6%;  $p = 0.18$ ). In the standard oral/IUI group, the chance of clinical pregnancy per cycle was 7.3% (30/411), 12.2% (37/304), 8.9% (21/236), 7.9% (12/156), in the first through fourth cycle respectively with continued similar rates (with diminished number of cycles) until the 9<sup>th</sup> cycle. Similarly, in the combo/IUI group, similar rates of pregnancy per cycle were seen up through the 8<sup>th</sup> cycle. Natural cycle/TDI cycles had significantly higher clinical pregnancy rates than either oral/IUI or combo/IUI cycles, as would be expected in this group without a history of infertility ( $p < 0.01$ ).

Protocol	+ hcg	Ongoing clinical pregnancy	Clinical Miscarriage	Chemical	Cancelled
Oral meds /IUI (n = 1365)	149 (10.9%)	112 (8.2%)	14 (1.0%)	21 (1.5%)	50 (3.7%)
Combo/IUI (n = 971)	94 (9.7%)	64 (6.6%)	18 (1.9%)	11 (1.1%)	44 (4.5%)
Natural/TDI (n=127)	30 (23.6%)	22 (16.1%)	4 (3.1%)	3 (2.4%)	2 (1.6%)

**Conclusion:** There does not appear to be an added benefit to adding 1-2 doses of gonadotropins to the standard oral medication/IUI protocol, however, this data supports that if a patient is hesitant to move to IVF, it is reasonable to consider another 3-4 standard protocol oral medication/IUI cycles with similar, albeit low, pregnancy rates to initial cycles.

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