

# Gonadotropin Ovulation Induction (OI) and Intrauterine Insemination (IUI): An Outdated Therapy

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## Abstract

Traditionally, ovulation induction (OI) with intrauterine insemination (IUI) has been a strategy used to maximize pregnancy outcomes in patients attempting pregnancy. A common pattern of performing OI/IUI historically has been to begin OI using oral medications, such as Clomiphene Citrate or Letrozole, and then escalating medical management to include injectable Gonadotropins such as follicle stimulating hormone (FSH). However, current medical literature shows Gonadotropin IUI to be associated inferior to other available fertility therapies in terms of both medical risks and cost effectiveness. Therefore, Gonadotropin IUI is now thought to be a suboptimal intervention for many patients. Based on current medical literature, the role of Gonadotropin IUI is likely to continually decline in the future. This trend will benefit patients by decreasing medical risks and increasing the cost effectiveness of fertility treatments.

## Introduction

Fertility therapies focus on maximizing the chances of achieving pregnancy. Because of the expense associated with such therapies, a focus on efficiency is central as to which interventions are offered to patients [1]. Consequently, infertility treatments are often offered in a “stepwise” fashion, escalating from more minimal therapies, such as ovulation induction (OI) with oral agents, to more aggressive therapies such as in-vitro fertilization (IVF) [1,2]. For most all therapies there are diminishing returns on any given intervention with repeated cycles of use. Most interventions, including IUI and IVF, began to become less effective after 3 or 4 failed trials [3].

Traditionally, OI/IUI has been a strategy used to maximize pregnancy outcomes in patients attempting pregnancy [2,4]. This is essentially an augmented natural cycle. Often an IUI cycle will begin with OI in which the ovaries are stimulated to produce more than one egg and higher hormone levels. Following ovulation of these eggs, the entire ejaculate is obtained and the motile sperm isolated and transferred at the appropriate time into the uterine cavity. Therefore, many more motile sperm are present than would be likely following natural intercourse. Thus, an OI-IUI cycle, or part thereof, is designed to create a ‘perfect storm’ of conditions in which many individuals who may be simply sub-fertile may achieve pregnancy in an accelerated manner.

## OI/IUI: Patterns of Utilization

A common pattern of performing OI/IUI historically has been to begin OI using oral medications, such as Clomiphene Citrate or Letrozole, and then escalating medical management to include injectable Gonadotropins such as follicle stimulating hormone (FSH) [1]. This pattern of escalating OI medications emerged decades ago when the success rates associated with IVF were much lower than they are today [5]. Additionally, the concern surrounding the rate of multiple gestation pregnancies was relatively muted in past decades in both the general population and among medical professionals [3,6,7].

## Concerns with Gonadotropin OI/IUI

The use of Gonadotropins for OI in the setting of IUI is now thought to be a problematic intervention by many experts [3,6,7]. The principal reasons for this are the increased risks and decreased efficiency, in terms of cost per percentage chance of achieving pregnancy, as compared to oral agent OI-IUI and IVF. The incidence of multiple gestation pregnancies is markedly higher in Gonadotropin OI-IUI as compared

to both oral agent OI/IUI and IVF [2,4,8,9]. In addition Gonadotropin IUI is much more likely to result in high order multiples (triplets, quadruplets, etc) than are other forms of fertility treatment [2,4,6,10]. In terms of controlling the rate of multiple gestations, IVF allows the most control over the risk of multiples as a single embryo may be transferred into the uterus, driving the rate of multiples in the setting of a single embryo transfer to less than 1% [11,12]. In contrast, Gonadotropin IUI may result in high order multiples due to the fact that this stimulation strategy recruits multiple eggs with a heightened chance for high order multiples. The TV program “John and Kate plus Eight” focused on a sextuplets pregnancy that resulted from Gonadotropin IUI [13].

The risks associated with high order pregnancies are many. The vast majority of obstetrical complications are markedly increased in multiple gestation pregnancies and these risks steadily rise with the number of gestations within the pregnancy [8]. In other words, a twin pregnancy is much higher risk than a singleton pregnancy and a triplet pregnancy is much higher risk than a twin pregnancy [8]. Serious obstetrical risks include preterm labor, miscarriage, low birth weight, pre-eclampsia, and gestational diabetes. In many high order pregnancies, one or more of the babies do not survive or are handicapped [8]. Therefore, reducing the rate of multiple gestation pregnancies has been a central focus within reproductive medicine in recent years [11]. Currently, Gonadotropin OI/IUI is the chief cause of high orders multiples [8,10,11,13]. Consequently, many experts have referred to the routine practice of Gonadotropin OI/IUI as an intervention that should be discontinued due to its associated risks [3,7].

In addition to an elevated risk profile, the utility of Gonadotropin OI/IUI as compared to other interventions has been questioned in terms of cost effectiveness. A common defense for the use of Gonadotropin OI/IUI

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IUI is that this therapy is less expensive than IVF. While this statement is true, Gonadotropin OI/IUI is still quite costly, averaging \$2-3,000 per cycle in the United States. IVF is more expensive, at \$10-15,000 per cycle, but also is associated with a much higher chance for achieving pregnancy [13]. A recent study comparing the cost effectiveness, the chance of pregnancy for each dollar spent, of various interventions in the setting of infertility found that oral agent OI/IUI was cost effective for 3 cycles after which time, the most cost effective strategy was to proceed with IVF as opposed to Gonadotropin IUI [3,7]. In other words, the study found that Gonadotropin IUI was more expensive per dollar spent than IVF.

## Summary

Gonadotropin IUI as a mainstay therapy for most infertility patients is a practice pattern that is decreasing in use by many reproductive health physicians. In many patients, Gonadotropin IUI is associated with an increased risk profile and inferior cost effectiveness compared to other treatment options. There are certain clinical situations where Gonadotropin IUI is a logical therapy. However, the widespread use of this intervention for most patients undergoing fertility treatment is problematic. Based on current medical literature, the role of Gonadotropin IUI is likely to continually decline in the future. This trend will benefit patients by decreasing medical risks and increasing the cost effectiveness of fertility treatments.

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