Research Article

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Pregnancy and Live Birth Rate Among Infertile Couples: A Comparison Between GnRH Agonist and Antagonist Protocols

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Abstract

Objective: To compare clinical pregnancy, live birth, pregnancy loss, and ovarian hyperstimulation outcomes among infertile couples undergoing intracytoplasmic sperm injection (ICSI) using either a GnRH agonist long protocol or a GnRH antagonist protocol.

Methods: This retrospective comparative study evaluated 194 ICSI cycles with complete outcome data (98 agonist, 96 antagonist). Categorical outcomes were compared using chi-square or Fisher's exact tests as appropriate. To strengthen interpretation of the primary endpoints, crude relative risks (RRs) with 95% confidence intervals (CIs) were calculated from the observed counts.

Results: The GnRH antagonist protocol was associated with a higher clinical pregnancy rate than the GnRH agonist long protocol (65.6% vs. 21.4%; RR 3.06, 95% CI 2.04–4.60; $p < 0.001$). Aggregate live birth was also higher in the antagonist group (42.7% vs. 8.2%; RR 5.23, 95% CI 2.59–10.57; $p < 0.001$). Pregnancy losses occurred in both groups; however, detailed category-specific comparisons were interpreted cautiously because of sparse cells. Ovarian hyperstimulation syndrome was infrequent in both groups and did not differ significantly between protocols.

Conclusion: In this retrospective cohort, GnRH antagonist stimulation was associated with improved clinical pregnancy and live birth outcomes without an observed increase in OHSS. Because the study was non-randomized and unadjusted, these findings should be interpreted as associative rather than causal, but they support further prospective evaluation of antagonist-based stimulation in routine ICSI practice.

Keywords: clinical pregnancy, live birth, GnRH antagonist, GnRH agonist, intracytoplasmic sperm injection, controlled ovarian stimulation, ovarian hyperstimulation syndrome

1. INTRODUCTION

Infertility affects a substantial proportion of couples of reproductive age and remains an important medical, psychological, and social problem worldwide. Assisted reproductive technologies (ART), particularly in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), have become established therapeutic options for many causes of infertility. Within ART, controlled ovarian stimulation (COS) remains a central determinant of treatment performance because it influences follicular recruitment, oocyte availability, embryo development, treatment burden, and the likelihood of pregnancy and live birth [1, 2, 3, 4].

Two of the most widely used COS strategies in contemporary IVF practice are the long gonadotropin-releasing hormone (GnRH) agonist protocol and the GnRH antagonist protocol. The agonist long protocol achieves pituitary downregulation after an initial flare effect, whereas the antagonist protocol produces rapid and reversible suppression of luteinizing hormone secretion through competitive receptor blockade [2, 4]. These pharmacological differences may influence treatment duration, gonadotropin exposure, cycle convenience, endometrial receptivity, and the balance between efficacy and safety.

Randomized trials and systematic reviews have compared GnRH agonist and antagonist regimens for more than two decades [1, 3, 5]. Much of that literature has focused on intermediate endpoints such as oocyte yield, embryo quality, or stimulation characteristics, while the comparative effects on patient-centered outcomes such as clinical pregnancy and live birth have remained less consistent across settings [3, 5, 6]. In addition, outcome patterns may differ across routine-care populations because of variation in patient selection, clinical protocols, and local practice environments.

The present study therefore focuses specifically on clinically meaningful outcomes in a real-world ICSI cohort. Using retrospective cycle-level data, we compared clinical pregnancy, detailed pregnancy outcomes, live birth, and ovarian hyperstimulation syndrome (OHSS) between GnRH agonist and GnRH antagonist stimulation. The principal contribution of this analysis is not to establish causality, but to quantify the magnitude and direction of associations observed in routine practice and to assess whether these associations are large enough to justify further prospective confirmation.

2. MATERIALS AND METHODS

2.1. DESIGN OF THE STUDY

This study was designed as a retrospective comparative analysis of infertile couples who underwent ICSI after controlled ovarian stimulation with either a GnRH agonist long protocol or a GnRH antagonist protocol.

2.2. RESEARCH POPULATION

A total of 200 ICSI cycles were initially identified and classified according to the ovarian stimulation protocol used.

GnRH agonist long protocol group: 100 cycles

GnRH antagonist protocol group: 100 cycles

Only cycles with complete clinical outcome data were included in the final analysis. Cycles with incomplete outcome ascertainment were excluded from the analytical sample.

2.3. OVARIAN STIMULATION PROTOCOLS

Patients in the agonist group underwent a conventional GnRH agonist long protocol that included pituitary downregulation followed by gonadotropin-induced controlled ovarian stimulation.

Patients in the antagonist group underwent gonadotropin stimulation with concurrent GnRH antagonist administration to prevent a premature luteinizing hormone surge.

Final oocyte maturation, oocyte retrieval, ICSI fertilization, embryo culture, and embryo transfer were performed according to the standard clinical procedures of the treating center.

2.4. OUTCOME MEASURES

The primary outcomes of interest were clinical pregnancy and live birth.

Clinical pregnancy was defined operationally in the dataset as a positive pregnancy outcome after embryo transfer. Live birth outcomes were further described as singleton live birth or twin live birth.

Secondary outcomes included pregnancy loss (abortion and ectopic pregnancy), ongoing pregnancy, absence of pregnancy, and the occurrence of ovarian hyperstimulation syndrome (OHSS).

2.5. INFORMATION GATHERING

Clinical outcome data were retrieved from patient medical records and embryology-related databases. The present article was designed as a focused clinical-outcome analysis; therefore, detailed stimulation variables, embryological development variables, and intermediate laboratory outcomes were not reanalyzed here. This scope should be considered when interpreting the findings, because unmeasured differences between groups cannot be excluded in a retrospective comparison.

2.6. ANALYSIS OF STATISTICS

Categorical outcomes were summarized as frequencies and percentages. The primary comparison of clinical pregnancy (positive vs. negative) between protocols was analyzed using a 2×2 chi-square test, for which assumptions were satisfied. Fisher's exact testing was used when sparse cells were present or when a more conservative exact comparison was preferable. To strengthen the interpretation of the principal binary endpoints, crude relative risks (RRs) and 95% confidence intervals (CIs) were derived from the observed counts. All statistical tests were two-sided, and p-values below 0.05 were considered statistically significant.

2.7. ETHICAL CONSIDERATIONS

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient confidentiality was maintained throughout data extraction and analysis. In keeping with institutional policy for retrospective review of existing clinical records, individual informed consent was waived.

3. RESULTS

3.1. STUDY POPULATION

The final analysis included 194 ICSI cycles with complete pregnancy outcome data: 98 cycles in the GnRH agonist long protocol group and 96 cycles in the GnRH antagonist protocol group. Because this was a focused outcome analysis, detailed baseline covariates and stimulation characteristics are not re-tabulated here; accordingly, the results should be interpreted as unadjusted between-group comparisons.

3.2. OUTCOMES OF CLINICAL PREGNANCY

A statistically significant difference in clinical pregnancy was observed between the two stimulation protocols. In the GnRH agonist group, 21 of 98 cycles (21.4%) resulted in a positive pregnancy outcome, whereas 77 of 98 cycles (78.6%) did not. In the GnRH antagonist group, 63 of 96 cycles (65.6%) resulted in pregnancy and 33 of 96 cycles (34.4%) did not.

The absolute difference in clinical pregnancy was 44.2 percentage points in favor of the antagonist protocol. The crude relative risk of pregnancy for antagonist versus agonist stimulation was 3.06 (95% CI 2.04–4.60), indicating that pregnancy was approximately three times more frequent in antagonist cycles in this retrospective cohort. Table 1 outlines the study outcome protocol.

Table 1. *Outcome Protocol*

Pregnancy result	GnRH agonist n (%)	GnRH antagonist n (%)	Total
Negative	77 (78.6)	33 (34.4)	110
Positive	21 (21.4)	63 (65.6)	84
Pearson chi-square = 38.58; $p < 0.001$.			

These findings identify a large between-group difference in favor of the antagonist protocol, although the retrospective and unadjusted design precludes causal attribution.

3.3. DISTRIBUTION OF LIVE BIRTH AND PREGNANCY OUTCOMES

Pregnancy outcomes were further described as singleton live birth, twin live birth, ongoing pregnancy, abortion, ectopic pregnancy, and no pregnancy. The antagonist group contributed a larger number of live births, whereas no pregnancy remained the dominant outcome in the agonist group.

Because several detailed categories had small cell counts, the six-category distribution in Table 2 was interpreted descriptively rather than through an overextended omnibus significance test. However, when the table was collapsed to the clinically important endpoint of any live birth versus no live birth, the antagonist protocol remained strongly favored (41/96, 42.7% vs. 8/98, 8.2%; RR 5.23, 95% CI 2.59–10.57; Fisher's exact $p < 0.001$).

Table 2. *Detailed pregnancy and live birth outcomes by protocol*

Outcome	GnRH agonist n (%)	GnRH antagonist n (%)	Total
Single live birth	6 (6.1)	31 (32.3)	37
Twin live birth	2 (2.0)	10 (10.4)	12
Ongoing pregnancy	4 (4.1)	5 (5.2)	9
Abortion	8 (8.2)	15 (15.6)	23
Ectopic pregnancy	1 (1.0)	2 (2.1)	3
No pregnancy	77 (78.6)	33 (34.4)	110

3.4. OUTCOMES OF MULTIPLE PREGNANCIES

Twin live birth was more frequent in the antagonist group (10.4%) than in the agonist group (2.0%). Given the modest cell counts, this observation is best regarded as descriptive. The more important clinical pattern is that the overall increase in live birth in the antagonist group was driven primarily by a rise in singleton live birth as well as twin live birth.

The occurrence of ovarian hyperstimulation syndrome (OHSS) was low in both cohorts and did not differ significantly between protocols (chi-square p = 0.370; Fisher's exact p = 0.537). Table 3 shows the number of hyperstimulation events observed in each protocol.

Table 3. *The number of times hyperstimulation happened via protocol*

Hyperstimulation	GnRH agonist n (%)	GnRH antagonist n (%)	Total
Mild–moderate	7 (7.1)	4 (4.2)	11
None	91 (92.9)	92 (95.8)	183

Accordingly, the better pregnancy and live birth outcomes observed with the antagonist protocol in this cohort were not accompanied by an apparent increase in OHSS.

3.5. SUMMARY OF IMPORTANT RESULTS

The GnRH antagonist protocol was associated with a markedly higher clinical pregnancy rate than the GnRH agonist long protocol.

Aggregate live birth, including both singleton and twin live birth, was also substantially more frequent in the antagonist group.

OHSS was uncommon in both groups and did not differ significantly between protocols.

4. DISCUSSION

In this retrospective ICSI cohort, the GnRH antagonist protocol was associated with substantially higher clinical pregnancy and live birth frequencies than the GnRH agonist long protocol, while OHSS remained uncommon in both groups. The magnitude of the crude differences was large, particularly for the two most clinically important endpoints: clinical pregnancy and live birth. These findings suggest that antagonist-based stimulation may perform favorably in this practice setting, but the observational design requires cautious interpretation.

4.1. PREGNANCY RATE AS A MAIN CLINICAL ENDPOINT

Clinical pregnancy remains one of the principal markers of IVF effectiveness. In the present study, pregnancy was achieved in 65.6% of antagonist cycles compared with 21.4% of agonist cycles, corresponding to a crude RR of 3.06. This direction of association is consistent with the broader literature showing that antagonist protocols can achieve reproductive outcomes at least comparable to long agonist protocols while offering practical and safety advantages [1, 3, 4, 5]. At the same time, the size of the observed difference in our cohort is larger than is commonly reported in pooled comparative studies, which reinforces the need to interpret the estimate as center-specific and potentially influenced by unmeasured clinical differences.

Earlier comparative studies often found similar pregnancy rates between agonist and antagonist protocols, whereas later analyses have highlighted circumstances in which antagonist-based stimulation performs at least as well clinically, with reduced treatment burden and lower risk of excessive ovarian response [3, 5]. The present findings add real-world evidence from an underrepresented clinical setting and suggest that protocol selection may be associated with meaningful differences in patient-centered outcomes in routine practice.

4.2. RESULTS OF LIVE BIRTH AND THEIR CLINICAL SIGNIFICANCE

Live birth is the most clinically meaningful endpoint in assisted reproduction. In the present dataset, live birth occurred in 42.7% of antagonist cycles and 8.2% of agonist cycles after aggregation of singleton and twin births. Even after adopting a conservative exact test for this binary comparison, the difference remained statistically strong. The antagonist group's advantage was not confined to one subtype of delivery, because both singleton and twin live births were more frequent.

The larger rise in singleton live birth is especially relevant clinically, as singleton birth remains the preferred reproductive endpoint for most couples and clinicians. Nevertheless, because embryo transfer practice and other cycle-level determinants were not reanalyzed in this focused outcome paper, the mechanism underlying the higher live birth frequency cannot be identified from the present data alone.

4.3. PREGNANCY LOSS AND SAFETY FACTORS

Pregnancy loss, including abortion and ectopic pregnancy, was observed in both groups. The antagonist group showed higher absolute numbers of loss, but this must be interpreted in the context of the much larger number of established pregnancies in that group. When loss was considered among pregnancies rather than across all cycles, the difference was not statistically persuasive in this dataset, and the small numbers limit firm inference. Thus, the current results do not support a confident conclusion that one protocol materially altered the risk of pregnancy loss.

OHSS occurred infrequently in both groups and no significant between-group difference was detected. This result is directionally compatible with prior literature indicating that GnRH antagonist protocols have a favorable safety profile, particularly with respect to excessive ovarian response [3, 5, 7]. In the present cohort, the main safety message is that the apparent reproductive advantage of antagonist stimulation was not offset by a detectable increase in OHSS.

4.4. COMPARISON WITH THE LITERATURE THAT IS ALREADY OUT THERE

The current findings broadly align with systematic reviews and comparative clinical studies reporting that GnRH antagonist regimens can achieve clinical pregnancy and live birth outcomes comparable to, and in some settings better than, those obtained with long agonist protocols [1, 3, 4, 5]. Our analysis differs from work centered primarily on surrogate laboratory endpoints because it emphasizes outcomes that matter most to patients and clinicians, namely pregnancy, live birth, and treatment safety.

At the same time, the present study should not be interpreted as overturning the broader comparative literature. Rather, it provides a practice-based signal that antagonist stimulation may have been associated with superior outcomes in this cohort. Future prospective studies with fuller baseline adjustment or random allocation would be needed to determine whether the observed differences persist after more rigorous control of confounding.

4.5. PROS AND CONS

A major strength of this study is its emphasis on clinically relevant outcomes drawn from routine ICSI practice. The analysis also includes an explicit safety comparison and now reports effect-size estimates for the main binary endpoints, which improves the interpretability of the observed differences.

Several limitations remain important. First, the retrospective non-randomized design limits causal inference. Second, the present paper does not re-tabulate detailed baseline covariates, stimulation characteristics, or embryo-transfer variables, so residual confounding cannot be excluded. Third, some outcome categories were sparse, which restricted category-specific statistical testing. Fourth, the analysis was conducted at the cycle level and should therefore be interpreted as a cohort comparison within this dataset rather than as definitive evidence of protocol superiority. These limitations do not eliminate the observed signal, but they do require caution in the strength of the conclusions.

4.6. CLINICAL CONSEQUENCES

From a clinical perspective, the data suggest that GnRH antagonist stimulation may represent an effective option for ICSI cycles in routine practice, particularly when the goals are to maximize pregnancy and live birth while maintaining a low incidence of OHSS. However, treatment selection should continue to be individualized according to patient characteristics, ovarian reserve, prior response history, and local clinical expertise.

5. CONCLUSION

In conclusion, this retrospective study found that the GnRH antagonist protocol was associated with higher clinical pregnancy and live birth rates than the GnRH agonist long protocol among infertile couples undergoing ICSI, without an observed increase in OHSS. These findings support the clinical relevance of antagonist-based stimulation in routine

practice; however, because the analysis is observational and unadjusted, the results should be viewed as hypothesis-generating evidence rather than definitive proof of superiority. Larger prospective studies with comprehensive covariate adjustment are warranted to confirm the magnitude and generalizability of these associations.

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