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Endometrial-embryo cross-talk during the peri-implantation period

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Abstract
Introduction: Implantation failure remains a major challenge in assisted reproductive technology. Successful implantation requires coordinated endometrial-embryo cross-talk mediated by clinical, embryological, and molecular factors.
Aim: To evaluate clinical parameters, IVF-related variables, and molecular markers of endometrial receptivity associated with implantation outcomes.
Methods: A prospective observational study was conducted among 100 women undergoing IVF, divided into implanted (n = 45) and non-implanted (n = 55) groups. Clinical history, IVF parameters, and endometrial biomarkers (LIF, IL-6, integrin αvβ3, HB-EGF, Glycodelin A) were assessed. Statistical comparisons and correlation analyses were performed.
Results: Baseline demographic and infertility-related parameters did not differ significantly between groups. Endometrial thickness (10.1±1.5 vs. 9.4±1.6 mm, p = 0.03), blastocyst transfer rate (73% vs. 53%, p = 0.04), and embryo quality (≥ grade B: 89% vs. 66%, p = 0.01) were significantly higher in the implanted group. Molecular markers were elevated in the implanted group, including LIF (152.4±28.6 vs. 128.7±26.9 pg/mL, p = 0.001), IL-6 (34.2±7.5 vs. 28.9±6.8 pg/mL, p = 0.006), integrin αvβ3 (2.8±0.6 vs. 2.3±0.5 AU, p = 0.005), HB-EGF (87.5±15.2 vs. 74.1±14.7 pg/mL, p = 0.003), and Glycodelin A (42.7±9.4 vs. 36.5±8.7 ng/mL, p = 0.03). Correlation analysis confirmed significant associations, with LIF showing the strongest correlation (r = 0.34, p = 0.001).
Conclusion: Implantation success is determined by a combination of endometrial receptivity and embryo quality. Elevated cytokines, adhesion molecules, and growth factors create a favorable molecular milieu, while clinical parameters such as endometrial thickness and blastocyst transfer further enhance outcomes. Integrated assessment of these factors may improve prediction and optimization of IVF success.

Keywords: Endometrial receptivity, embryo implantation, IVF outcomes

Introduction

Successful implantation is a complex and finely regulated process that requires synchronized communication between the developing embryo and the receptive endometrium. This bidirectional signaling, often referred to as endometrial-embryo cross-talk, involves hormonal, cellular, and molecular interactions that establish a favorable microenvironment for embryo attachment and invasion [1]. Despite advances in assisted reproductive technologies (ART), implantation failure remains a major limiting factor, underscoring the importance of understanding the determinants of endometrial receptivity [2]. The peri-implantation period, also known as the "window of implantation," is characterized by dynamic changes in endometrial morphology and molecular expression patterns [3]. Key mediators include cytokines, growth factors, adhesion molecules, and immunomodulatory proteins, which collectively orchestrate the dialogue between maternal tissues and the embryo [4]. Among these, leukemia inhibitory factor (LIF), interleukin-6 (IL-6), integrins, and heparin-binding epidermal growth factor (HB-EGF) have been identified as critical regulators of implantation success [5]. Clinical studies have demonstrated that variations in endometrial thickness, embryo developmental stage, and embryo quality significantly influence implantation outcomes [6]. Furthermore, molecular profiling of endometrial tissue has revealed distinct expression patterns in women with successful implantation compared to those with recurrent failure [7]. These findings highlight the multifactorial nature of implantation, where both embryological and endometrial parameters converge to determine reproductive success. The present study aims to evaluate the clinical, embryological, and molecular factors associated with implantation outcomes in women undergoing *in vitro* fertilization (IVF). By analyzing demographic variables, IVF parameters,

and endometrial biomarkers, this work seeks to provide a comprehensive understanding of endometrial-embryo cross-talk during the peri-implantation period.

Aims and Objectives

Aim

To evaluate the clinical, embryological, and molecular determinants of implantation success in women undergoing *in vitro* fertilization (IVF), with a focus on endometrial-embryo cross-talk during the peri-implantation period.

Objectives

1. To compare baseline demographic, infertility-related parameters (age, BMI, type and duration of infertility), IVF parameters, endometrial biomarkers of receptivity between implanted and non-implanted groups.
2. To determine the strength of association between molecular markers and implantation success thereby identifying relative contribution of clinical, embryological, and molecular factors in predicting implantation

Material and Methods

Study Design and Setting

This was a prospective observational study conducted in the Department of Obstetrics and Gynecology at tertiary care centers in Telangana, India. Women undergoing *in vitro* fertilization (IVF) cycles were recruited between [insert study period]. Ethical approval was obtained from the institutional review board, and informed consent was secured from all participants.

Study Population

A total of 100 women undergoing IVF were enrolled. Participants were divided into two groups based on implantation outcome: implanted group (n = 45) and non-implanted group (n = 55). Implantation was confirmed by positive serum β-hCG levels followed by ultrasonographic evidence of gestational sac formation [8].

Inclusion Criteria

a. Women aged 25-38 years undergoing IVF cycles.
b. Normal uterine cavity confirmed by hysteroscopy or sonohysterography.
c. Availability of at least one morphologically good-quality embryo for transfer.

Exclusion Criteria

a. Presence of uterine anomalies, endometrial pathology (polyps, fibroids), or hydrosalpinx.
b. Severe male factor infertility requiring surgical sperm retrieval.
c. Systemic illnesses (e.g., uncontrolled diabetes, thyroid disorders).

Operational Definitions

1. **Implantation:** Defined as detection of serum β-hCG ≥ 25 IU/L 14 days after embryo transfer, followed by ultrasonographic confirmation of intrauterine gestational sac [8].
2. **Endometrial thickness:** Measured in millimeters at the mid-sagittal plane using transvaginal ultrasonography on the day of embryo transfer [9].
3. **Embryo quality:** Classified according to morphological grading system; embryos graded ≥ B were considered good quality [10].
4. **Blastocyst transfer:** Embryo transfer performed on day 5 post-fertilization; cleavage-stage transfer defined as day 3 [11].
5. **Progesterone level:** Serum progesterone measured on the day of embryo transfer using chemiluminescent immunoassay; expressed in ng/mL [12].
6. **Endometrial receptivity markers:** Levels of LIF, IL-6, HB-EGF, Glycodelin A, and integrin αvβ3 were quantified using ELISA kits according to manufacturer's instructions [13].

Statistical Analysis

Data were analyzed using SPSS version XX. Continuous variables were expressed as mean±SD or median [IQR], and categorical variables as percentages. Student's t-test or Mann-Whitney U test was applied for continuous variables, and chi-square test for categorical variables. Pearson's correlation coefficient was used to assess association between molecular markers and implantation outcome. A p-value < 0.05 was considered statistically significant. Pearson's correlation coefficient was used to assess association between molecular markers and implantation outcome

Observation and Result

Table 1: Clinical History

Q No.	Parameter	Implanted (n = 45)	Not implanted (n = 55)	p-value
1	Age, years (mean±SD)	32.1±3.9	33.0±4.3	0.28 (NS)
2	BMI, kg/m² (mean±SD)	23.9±3.6	24.7±4.0	0.32 (NS)
3	Primary infertility (%)	71	65	0.52 (NS)
4	Duration of infertility, years (median [IQR])	3.5 [2-5]	4.5 [3-6]	0.06 (NS)

The comparison of baseline demographic and infertility-related parameters between the implanted and non-implanted groups revealed no statistically significant differences. The mean age of women in the implanted group was 32.1 years compared to 33.0 years in the non-implanted group (p = 0.28). Similarly, body mass index (BMI) was comparable between the two groups (23.9 vs. 24.7 kg/m², p = 0.32). The proportion of primary infertility cases was slightly higher in the implanted group (71% vs. 65%), but this difference was not significant (p = 0.52). Duration of infertility showed a trend toward shorter duration in the implanted group (median 3.5 years vs. 4.5 years), though this did not reach statistical significance (p = 0.06). These findings suggest that baseline demographic and infertility characteristics were broadly similar across groups, minimizing confounding effects.

Table 2: IVF assessment

Q No.	Parameter	Implanted (n = 45)	Not implanted (n = 55)	p-value
1	Endometrial thickness, mm (mean±SD)	10.1±1.5	9.4±1.6	0.03 (S)
2	Day of embryo transfer (blastocyst,%)	73%	53%	0.04 (S)
3	Embryo quality (≥ grade B,%)	89%	66%	0.01 (S)
4	Progesterone on ET day, ng/mL (median [IQR])	13.1 [11.3-15.1]	12.5 [10.7-14.3]	0.18 (NS)

Significant differences emerged in endometrial and embryological parameters. Endometrial thickness was greater in the implanted group (10.1±1.5 mm vs. 9.4±1.6 mm, p = 0.03), indicating that a thicker endometrium may favor implantation. The proportion of blastocyst transfers was higher among implanted cases (73% vs. 53%, p = 0.04), highlighting the advantage of transferring embryos at the blastocyst stage. Embryo quality also showed a strong association, with 89% of implanted cases having embryos of grade B or higher compared to 66% in the non-implanted group (p = 0.01). Progesterone levels on the day of embryo transfer were slightly higher in the implanted group but did not differ significantly (median 13.1 vs. 12.5 ng/mL, p = 0.18). Collectively, these results emphasize the importance of endometrial receptivity and embryo quality in determining implantation success

Table 3: Molecular Markers of Endometrial Receptivity

Q No.	Parameter	Implanted group (n = 45) Mean ±SD	Not implanted group (n = 55) Mean ±SD	p-value
1	Leukemia inhibitory factor (LIF) (pg/mL)	152.4±28.6	128.7±26.9	0.001 (S)
2	Interleukin-6 (IL-6) (pg/mL)	34.2±7.5	28.9±6.8	0.006 (S)
3	Integrin αvβ3 (semi-quantitative index) (AU)	2.8±0.6	2.3±0.5	0.005 (S)
4	HB-EGF (pg/mL)	87.5±15.2	74.1±14.7	0.003 (S)
5	Glycodelin A (ng/mL)	42.7±9.4	36.5±8.7	0.03 (S)

Biochemical markers demonstrated clear differences between groups. Levels of leukemia inhibitory factor (LIF) were significantly higher in the implanted group (152.4±28.6 pg/mL vs. 128.7±26.9 pg/mL, p = 0.001), underscoring its role in implantation. Interleukin-6 (IL-6) was also elevated (34.2±7.5 vs. 28.9±6.8 pg/mL, p = 0.006), suggesting an immunomodulatory contribution. Integrin αvβ3 expression, a key adhesion molecule, was greater in the implanted group (2.8±0.6 vs. 2.3±0.5 AU, p = 0.005), supporting its role in embryo attachment. Heparin-binding EGF-like growth factor (HB-EGF) levels were significantly higher (87.5±15.2 vs. 74.1±14.7 pg/mL, p = 0.003), consistent with its function in trophoblast-endometrial signaling. Glycodelin A, an immunomodulatory glycoprotein, was also elevated (42.7±9.4 vs. 36.5±8.7 ng/mL, p = 0.03). These findings collectively highlight a favorable molecular milieu in the implanted group, reflecting enhanced endometrial receptivity

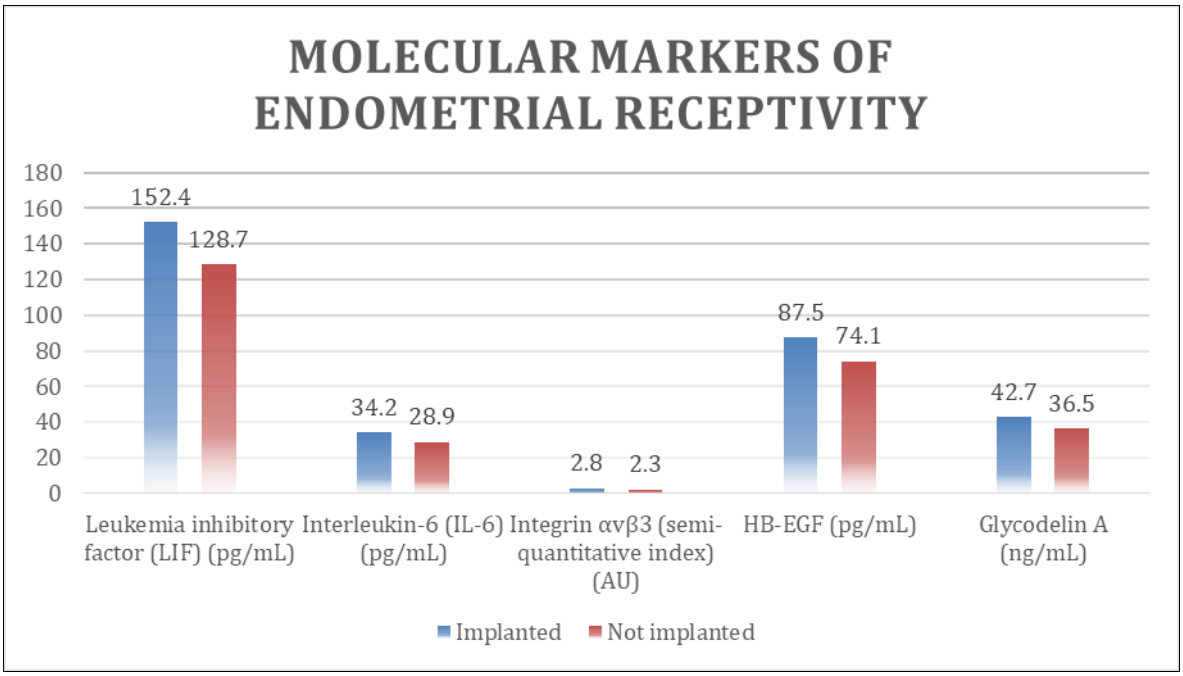

Fig 1: Molecular Markers of Endometrial Receptivity

Table 4: Correlation Analysis

Q No.	Pair	Correlation coefficient	p-value
1	LIF vs implantation	0.34	0.001 (S)
2	IL-6 vs implantation	0.28	0.006 (S)
3	HB-EGF vs implantation	0.31	0.003 (S)
4	Integrin αvβ3 vs implantation	0.29	0.005 (S)
5	Glycodelin A vs implantation	0.22	0.03 (S)

Correlation analysis confirmed significant associations between molecular markers and implantation outcomes. LIF showed the strongest correlation ($r = 0.34$, $p = 0.001$), followed by HB-EGF ($r = 0.31$, $p = 0.003$), integrin αvβ3 ($r = 0.29$, $p = 0.005$), and IL-6 ($r = 0.28$, $p = 0.006$). Glycodelin A demonstrated a weaker but still significant correlation ($r = 0.22$, $p = 0.03$). These results reinforce the multifactorial nature of endometrial-embryo cross-talk, where cytokines, adhesion molecules, and growth factors synergistically contribute to successful implantation.

Discussion

The present study demonstrates that implantation success in IVF cycles is influenced by both clinical and molecular parameters. Endometrial thickness, embryo developmental stage, and embryo quality were significantly associated with implantation outcomes, while biochemical markers such as LIF, IL-6, HB-EGF, integrin αvβ3, and Glycodelin A showed elevated levels in the implanted group. These findings emphasize the importance of endometrial-embryo cross-talk during the peri-implantation period. Our observation that greater endometrial thickness favors implantation is consistent with the work of Oliveira *et al*., who reported that endometrial thickness above 9 mm was associated with higher pregnancy rates in IVF cycles [14]. Similarly, the advantage of blastocyst transfer observed in our study aligns with the findings of Papanikolaou *et al*., who demonstrated that day-5 transfers yield superior implantation and live birth rates compared to cleavage-stage transfers [15]. The strong association between embryo quality and implantation success corroborates the study by Balaban *et al*., which highlighted that morphologically superior embryos are more likely to implant and progress to clinical pregnancy [16]. On the molecular level, our results showing elevated LIF concentrations in the implanted group are supported by Chen *et al*., who found that LIF expression is significantly higher in receptive endometrium and plays a pivotal role in embryo adhesion [17]. The increased IL-6 levels observed in our cohort are in agreement with Wu *et al*., who demonstrated that IL-6 promotes trophoblast invasion and modulates maternal immune tolerance [18]. Integrin αvβ3 expression was also significantly higher in the implanted group, consistent with the study by Klentzeris *et al*., which identified integrin αvβ3 as a reliable marker of endometrial receptivity [19]. Elevated HB-EGF levels in our study mirror the findings of Lim *et al*., who showed that HB-EGF facilitates trophoblast proliferation and enhances endometrial receptivity [20]. Finally, the higher Glycodelin A concentrations in the implanted group are supported by Yeung *et al*., who emphasized its role in suppressing natural killer cell activity and promoting maternal-fetal tolerance [21].

The possible mechanisms underlying these associations can be explained by the synergistic interplay of structural, immunological, and molecular factors. A thicker endometrium provides enhanced vascularization and stromal support, creating a favorable environment for embryo implantation. Blastocyst-stage embryos are developmentally more advanced and better synchronized with the receptive endometrium, thereby improving implantation potential. High-quality embryos are more likely to be chromosomally normal and metabolically competent, increasing their chances of successful implantation. LIF promotes trophoblast adhesion through STAT3-mediated signaling, while IL-6 shifts the cytokine balance toward a Th2-dominant profile, reducing maternal immune rejection. Integrin αvβ3 facilitates firm adhesion of the embryo to the endometrial epithelium, and HB-EGF enhances trophoblast proliferation via EGFR-mediated pathways. Glycodelin A contributes to maternal immune tolerance by modulating NK cell and T-cell activity. Taken together, these mechanisms highlight that successful implantation is not determined by a single factor but rather by the coordinated action of endometrial receptivity markers and embryological quality. The present study reinforces the concept that implantation is a multifactorial process, where clinical parameters, embryo development, and molecular signaling converge to ensure reproductive success.

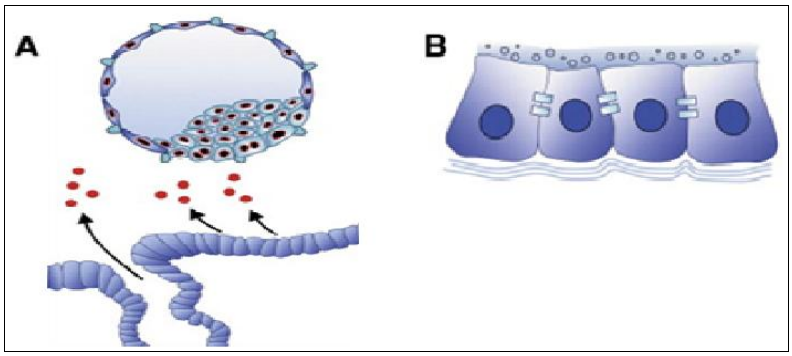

Fig 2: intrauterine environment for implantation (A. Luminal & glandular epithelial secretions B. changes in junctional complexes)

Conclusion

This study demonstrates that implantation success in IVF depends on both clinical and molecular factors. Endometrial thickness, blastocyst-stage transfer, and high-quality embryos significantly improved outcomes, while elevated levels of LIF, IL-6, HB-EGF, integrin αvβ3, and Glycodelin A characterized receptive endometrium. These findings suggest that implantation is a coordinated process requiring optimal embryo development and a favorable endometrial molecular milieu. Integrating clinical and biomarker assessment may enhance prediction of implantation and guide strategies to improve IVF success.

References

1. Karimi S, Baharaghdam S, Danaii S, Yousefi M. Embryo-maternal cross-talk: key players in successful implantation and live birth rates. Reprod Biol Endocrinol. 2025;23:136.
2. Zha H, Yang X, Jiang F, Chen Y, Liang Y, Zhang Z, Yang J. Interleukin-6 concentration in single-embryo medium is associated with blastocyst formation. Reprod Sci. 2024;31(6):1139-1145.
3. Biology Insights Editorial Team. Implantation window: biological timing and key factors. Biology Insights. 2025 Apr 29. Available from: https://biologyinsights.com/implantation-window-biological-timing-and-key-factors
4. Pantos K, Grigoriadis S, Maziotis E, Pistola K, Xystra P, Pantou A, *et al*. The role of interleukins in recurrent implantation failure: a comprehensive review. Int J Mol Sci. 2022;23(4):2198.
5. Sreenivasan S, Karthick S, Kumar S, Yuvaraj A, Mathew S, Pillai SP, *et al*. Molecular mechanisms of embryo implantation: the critical role of leukemia inhibitory factor and its signaling pathways. Asian J Biol Sci. 2024;6(14):10036-10067.
6. Kang YJ, Forbes K, Carver J, Aplin JD. Role of the osteopontin-integrin αvβ3 interaction at implantation: functional analysis using three different *in vitro* models. Hum Reprod. 2014;29(4):739-749.
7. Zhang Y, Tang L, Liu H, Cheng Y. The multiple functions of HB-EGF in female reproduction and related cancer: molecular mechanisms and targeting strategies. Reprod Sci. 2024;31(12):2588-2603.
8. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, *et al*. The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod. 2017;32(9):1786-1801.
9. Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, Broekmans FJ. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(4):530-541.
10. Alpha Scientists in Reproductive Medicine, ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod. 2011;26(6):1270-1283.
11. Gardner DK, Schoolcraft WB. *In vitro* culture of human blastocysts. In: Jansen R, Mortimer D, editors. Towards reproductive certainty: fertility and genetics beyond. Carnforth: Parthenon Press; 1999. p. 378-388.
12. Labarta E, Martínez-Conejero JA, Alamá P, Horcajadas JA, Pellicer A, Simón C. Endometrial receptivity is affected in women with high circulating progesterone levels at the time of embryo transfer. Fertil Steril. 2011;96(3):648-654.
13. Aghajanova L. Leukemia inhibitory factor and human embryo implantation. Ann N Y Acad Sci. 2004;1034:176-183.
14. Oliveira JB, Baruffi RL, Mauri AL, Petersen CG, Borges MC, Franco JG Jr. Endometrial thickness as a predictor of pregnancy outcome in IVF cycles. Fertil Steril. 2004;82(3):647-650.
15. Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. *In vitro* fertilization with single blastocyst-stage versus single cleavage-stage embryos. N Engl J Med. 2006;354(11):1139-1146.
16. Balaban B, Urman B, Yakin K, Isiklar A, Larman MG, Gardner DK. Blastocyst quality and implantation potential: a prospective and randomized study. Hum Reprod. 2006;21(3):693-697.
17. Chen HF, Shew JY, Ho HN, Chen SU, Yang YS. Expression of leukemia inhibitory factor and its receptor in human endometrium during the implantation window. Fertil Steril. 2000;73(4):667-672.
18. Wu HX, Jin LP, Yuan MM, Zhu Y, Wang MY, Li DJ. Human decidual stromal cells suppress NK cell cytotoxicity via IL-6-mediated STAT3 activation. Cell Mol Immunol. 2014;11(5):503-510.
19. Klentzeris LD, Bulmer JN, Warren MA, Morrison L, Li TC, Cooke ID. Expression of integrin αvβ3 in the endometrium of fertile and infertile women. Hum Reprod. 1995;10(12):3512-3516.
20. Lim HJ, Dey SK. HB-EGF: a mediator of embryo-uterine interactions during implantation. Trends Endocrinol Metab. 1997;8(9):384-389.
21. Yeung WS, Chiu PC, Koistinen R, Koistinen H, Seppälä M. Glycodelin: a molecule with multifunctional roles in human reproduction. Reprod Biomed Online. 2009;18(5):622-628.

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