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ORIGINAL ARTICLE

Does Adenomyosis Influence ICSI Clinical Outcome? A Systematic Analysis and Impact of GnRH Agonist Pretreatment for Women with Adenomyosis in ICSI–FET Cycle: A Retrospective Cohort Study

Pradeepa Sudhakar[1] · **Saranya Manivannan**[1] · **Dhanabagyam Kandasamy**[2] · **Kavitha Jayapal**[3]

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Abstract

Objective To evaluate the impact of adenomyosis on pregnancy outcome in ICSI/FET cycles and the beneficial effect of GnRH agonist pretreatment, conservative surgery or combination therapy on pregnancy outcome.

Materials and Methods This is a retrospective cohort study where 613 ICSI cycles done in the period from Jan 2018 to Dec 2020 in Sudha infertility centre, Erode were analyzed. Study populations include 235 women with adenomyosis undergoing ICSI/FET cycle.

Result Overall, the outcome in terms of clinical pregnancy rate, miscarriage rate, live birth date and ongoing pregnancy rate was lower in women with adenomyosis following ICSI/FET cycles. We found significant improvement in clinical pregnancy rate who had pretreatment with GnRH agonist, conservative surgery or combination therapy.

Conclusion Adenomyosis as such has detrimental effect on ICSI clinical outcome. Pretreatment with GnRH agonist and conservative surgery and GnRH agonist long protocol could be beneficial. Further large scale prospective comparative studies are needed to confirm this result.

Keywords Adenomyosis · Pregnancy outcome · Systematic analysis · ICSI-FET cycles

Pradeepa Sudhakar is a Senior Consultant IVF and Reproductive Medicine, Department of Obstetrics and Gynecology, Sudha Hospital, Erode, Tamil Nadu, India; Saranya Manivannan is a Consultant IVF and Reproductive Medicine, Department of Obstetrics and Gynecology, Sudha Hospital, Erode, Tamil Nadu, India; Dhanabagyam Kandasamy is a Director, Department of Reproductive Medicine, Sudha Hospital, Coimbatore, Tamil Nadu, India.

✉ Pradeepa Sudhakar
sudharesearch2021@gmail.com

Saranya Manivannan
prinitha2004@yahoo.co.in

Dhanabagyam Kandasamy
sudhainfertility@gmail.com

Kavitha Jayapal
drkavithasubas@gmail.com

[1] Department of Obstetrics and Gynecology, Sudha Hospital, Erode, Tamil Nadu, India

[2] Department of Reproductive Medicine, Sudha Hospital, Tamil Nadu, Coimbatore, India

[3] Department of Obstetrics and Gynecology, Sudha Hospital, Tamil Nadu, Coimbatore, India

Introduction

Until recently, adenomyosis, a benign uterine disorder commonly found in women > 40 years (80%). Adenomyosis is found in high proportion (24.4%) in infertile women, along with endometriosis. Reports show that 20% are found in women < 40 years. As women delay their pregnancy, it is not uncommon to encounter adenomyosis in women seeking fertility treatment.

Adneomyosis is characterized by the presence of ectopic endometrial glands and stroma in uterine myometrium with reactive hyperplasia and hypertrophy of the surrounding myometrium leading to bulky uterus [1, 2]. The most common symptoms include menorrhagia (50%), dysmenorrhea (30%), meterorrhagia (20%).

In the last few years, several studies analyzed the impact of adenomyosis on fertility outcome following ART. Some studies reported no measurable impact, while others showed negative impact on pregnancy outcome following ICSI cycle. Few studies reported results in adenomyosis treated with GnRH agonist, conservative surgery or combined therapy. A live birth rate after treatment with GnRH agonist for

5 months was first reported by silva et al. in 1994 [17]. In another case report, Nelson and Corson in 1993 reported positive outcome in a patient with adenomysis who underwent GnRH agonist pretreatment Fujishita et al. in 2014 described conservative reductive surgery for adenomyosis. Kishi et al. in 2014 [14] demonstrated 60.8% of women with adenomyosis and IVF failure conceived after uterine sparing debulking conservative surgery. Wang et al. in 2009 also suggested laparoscopic cytoreductive surgery improves success rates in women with focal adenomyosis undergoing IVF/ICSI cycles. In one large prospective study, 55 of 165 patients with adenomyosis had pregnancy following GnRH agonist treatment or surgery or combination therapy [18].

Here, in our study, we analyzed the impact of adenomyosis on pregnancy outcome in 168 patients with adenomyosis who had GnRH agonist pretreatment. We found good pregnancy outcome with a significant P value of 0.020.

Materials and Methods

Study Design

This retrospective cohort study identified and reviewed the records of women with adenomyosis who underwent ICSI–FET cycles from Jan 2018 to December 2020 in the infertility clinic of Sudha Hospitals, Erode. Among 613 ICSI cycles, 235 patients had adenomyosis and had both GnRH agonist pretreatment or conservative surgery which includes adenomyomectomy for focal adenomyosis and debulking cytoreductive surgery for diffuse adenomyosis or combination therapy. All patients had GnRH agonist long protocol for their ICSI cycle followed by FET transfer. The sample of 235 cases was selected using Krejcie Morgan method, with the confidence level of 95% and the error margin of 5%.

Data and Statistical Analysis

Continuous data were analyzed for normality in frequentist statistics using the Shapiro–Wilk test, and the data were expressed as mean and standard deviation ($\mu \pm SD$), depending on the distribution. Categorical data were presented as occurrence and percentage within each study group. Inter variable differences were assessed using Mann–Whitney tests and chi-square tests for continuous and categorical data, respectively. Receiver-operating characteristic (ROC) curve analyses were used for the sensitivity and specificity estimates of the prognostic role of endometrial thickness, age of diagnosis, adenomyosis size, and AMH in identifying the likelihood of clinical pregnancy rate. Appropriate cut-offs aimed at maximizing both sensitivity and specificity were identified, a p value of <0.05 was considered statistically significant.

Model for Adoption

The association between GnRH agonist pretreatment for adenomyosis and pregnancy outcome was evaluated by binary logistic regression analysis while adjusting for potential confounders. Statistical significance level was set at p 0.05. Analyses were performed using IBM SPSS statistics 26.0

In binary logistic regression, we need to use a multifaceted formula and adapt back and forth from the logistic equation to the ordinary least square (OLS) type equation.

$$\ln\left(\frac{P}{1-P}\right) = a + bX \tag{1}$$

$$P = \frac{\exp(a+bX)}{1+\exp(a+bx)} = \frac{e^{a+bx}}{1+e^{a+bx}} \tag{2}$$

$$\begin{aligned}\hat{\psi} &= \frac{\text{Success versus failure when } X=1}{\text{Success versus failure when } X=0} \\ &= \frac{X=1 \text{ when } Y=1 / X=1 \text{ when } Y=0}{X=0 \text{ when } Y=1 / X=0 \text{ when } Y=0} \\ &= \frac{\pi(1)/1-\pi(1)}{\pi(0)/1-\pi(0)}\end{aligned} \tag{3}$$

Results

This was a retrospective study of women with adenomyosis and infertility undergoing ICSI/FET cycles in infertility clinic of Sudha Hospital between Jan 2018 to December 2020. All these women had GnRH agonist long protocol for ICSI cycle followed by FET cycle for their transfer. All these women had pretreatment with either GnRH agonist, conservative surgery or combination therapy.

Initial assessment had been done in their first visit which includes detailed history, infertility workup and a transvaginal ultrasound (TVS) [3, 9]. TVS done using 7.5 MHz probe and uterine and ovarian measurements were taken in three orthogonal planes and antral follicular count noted. Adenomyosis was diagnosed according to Naftalin et al. criteria [16].

Women with focal adenomyosis underwent adenomyomectomy surgery followed by GnRH agonist with Inj. Goserelinacetate 3.6 mg two to three doses and women with diffuse adenomyosis had GnRH agonist Inj.Goserelinacetate 3.6 mg two to three doses. Women with severe adenomyosis had conservative debulking surgery followed by GnRH agonist pretreatment [5, 7].

They had GnRH agonist long protocol for their ICSI cycle and embryos were frozen. Embryo transfer was done in FET

Table 1 Patient characteristics and pregnancy outcomes in adenomyosis by IVF/ICSI stimulation protocol

Parameters	CBR results		*p* value
	Positive (197)	Negative (38)	
Age	32.59 ± 4.95	35.06 ± 5.59	0.033**
BMI	24.72 ± 4.30	26.29 ± 4.99	0.017**
Endometrial thickness	0.96 ± 0.50	0.63 ± 0.21	0.047**
AMH	2.03 ± 2.35	1.53 ± 0.96	0.040**
TSH	2.88 ± 2.34	1.66 ± 0.80	0.031**
Early miscarriage	67 (97.1)	2 (2.9)	0.098
GnRH agonist	168 (96.6)	6 (3.4)	0.020**

** Significant at the 0.05 level (2-tailed)

Table 2 Results of logistic regression binary logistic regression analysis with clinical outcomes in adenomyosis classified in clinical symptoms and risk factors of the study population

Observed variables	β	SE	Wald	Sig	Exp(β)
Menorrhagia	− 1.165	1.124	2.073	**.030**	3.312
Dysmenorrhea	1.545	.922	2.809	**.004**	4.687
Early miscarriage	− 1.239	.819	2.289	.130	.290
Chocolate cyst	− 18.903	6683.993	.000	.998	.000
Constant	− 2.041	.325	39.460	.000	.130

Number of observation = 235

$\chi^2(7) = 5.251$

p value = 0.629

Log likelihood = 109.522

Cox and Snell $R^2 = 0.052$

Nagelkerke $R^2 = 0.128$

Model accuracy = 92.8%

cycles after 6 months to 1 year, following their surgery. Day 5 blastocyst transfers done and the results were seen after 12 days with β HCG value and confirmed by β HCG doubling after 48 h of the first value. Clinical pregnancy is confirmed a week later by seeing gestational sac in TVS and cardiac activity at 5 weeks. Miscarriage rate is assessed by pregnancy losses < 20 weeks. Ongoing pregnancy rate is taken as pregnancy continuing > 12 weeks. Live birth rate is by calculating live birth after 26 weeks of completed gestation [8, 15].

In our study among the 235 infertility couple diagnosed with adenomyosis, the median age was 33 years with the inter quartile range 36–38 years. Patients of age group 32.59 ± 4.59 had positive clinical pregnancy rate compared to 35.06 ± 4.95 age group with significant *p* value of 0.33. The median AMH is 1.5, and median BMI was 25 (Table 1).

A binary logistic regression was performed to assess the impact of several factors the clinical outcomes in adenomyosis in terms of clinical symptoms and risk factors of the study population. The model contains eight independent variables, as listed in Table 2. The full model containing all predictors was statistically not significant, chi-square = 5.251 ($N = 235$), $p = 0.629$, indicating that the model was not able to distinguish between the clinical outcomes in adenomyosis in terms of clinical symptoms and risk factors of the study population. The model as a whole explained between the Cox and Snell $R^2 = 0.052$ and Nagelkerke $R^2 = 0.128$ of the variance in consultation, and model accuracy 92.8 percent of cases. Furthermore, the log likelihood function = 109.522 and the proportions of samples correctly predicted for their likely status in the clinical outcomes in adenomyosis in clinical symptoms and risk factors of the study population both indicate a good fit of the equation. By far, the strongest predictor of adenomyosis classified in terms of clinical symptoms and risk factors are menorrhagia and dysmenorrhea and were statistically significant of $p = 0.004$ and $p = 0.030$ that the Wald test model fits value (4.687 and 3.312) is higher than other explanatory variables.

Clinical pregnancy rate, miscarriage rate, live birth rate and ongoing pregnancy rate are occur in women with combined adenomyosis and endometriosis than with adenomyosis alone. The success rates are significantly higher in women with adenomyosis who had GnRHa pre-treatment GnRHa long protocol. Among 235 patients, 204 patients had progressed till term and had a live birth rate of 73.24

Table 3 Comparison of clinical outcomes among the GnRH agonist protocol

Parameters	Adenomyosis (Group A)	Endometriosis + Adenomyosis (Group B)	*p* value
Clinical pregnancy rate *n* (%)	**179/213** 84.04%	**18/22** 81.82%	0.003*
Miscarriage rate/pregnancy *n* (%)	**7/213** 3.29%	**2/22** 9.09%	0.019**
Live birth rate *n* (%)	**156/213** 73.24%	**13/22** 59.09%	0.015**
Ongoing	**16/213** 7.51%	**3/22** 13.64%	0.016**

*Significant at the 0.01 level (2-tailed). **Significant at the 0.05 level (2-tailed)

percent. Ongoing pregnancy rate in adenomyosis group is 16 in 213 cases with an efficient p value of 0.16 (Table 3).

ROC curves show the probability of true-positive results (sensitivity) as a function of the probability of false positive results (1-specificity). For this cause, the cut-off point has to be set at each point of the assessment axis, and sensitivity and specificity must be considered for these points. The possible combinations of sensitivity and specificity obtained when the cut-off points are varied are combined to calculate the area under curve (AUC).

The AUC, calculated as sensitivity and specificity, is a measure that shows how ''good'' (AUC close to 1) or ''bad'' (AUC close to 0.5) a test is. As illustrated in Fig. 1, the ROC curves analysis revealed that AUC = 0.844, p value 0.000, the results for the retrospective studies remained significant (95% CI 0.739–0.950). It shows that endometrial thickness is a suitable factor for prediction of the result of IVF/ICSI, which was same as the Mann–Whitney test result. Moreover, in Fig. 2, the ROC curve analysis demonstrated that the cut-off value of age at diagnosis and clinical pregnancy rate stated that AUC = 0.619, p value = 0.103, the results for the retrospective studies remained not significant (95% CI 0.499–0.739). In Fig. 3, the ROC curve analysis confirmed that the cut-off value of the diagnostic thresholds of maximal adenomyosis size provided by ROC curve analysis for prediction of clinical pregnancy rate (AUC = 0.510, p value = 0.890) and the results for the retrospective studies remained not significant (95% CI 0.366–0.655). In Fig. 4, the ROC curve analysis confirmed that the cut-off value of the diagnostic prediction of AMH and FSH provided by ROC curve analysis for prediction of clinical pregnancy rate (AUC = 0.696, p value = 0.007) and the results

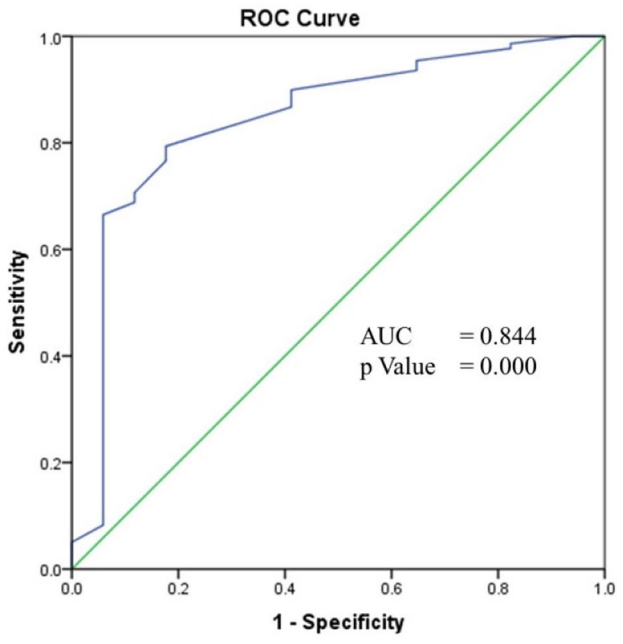

Fig. 1 The diagnostic thresholds of maximal endometrial thickness provided by ROC curve analysis for prediction of clinical pregnancy rate

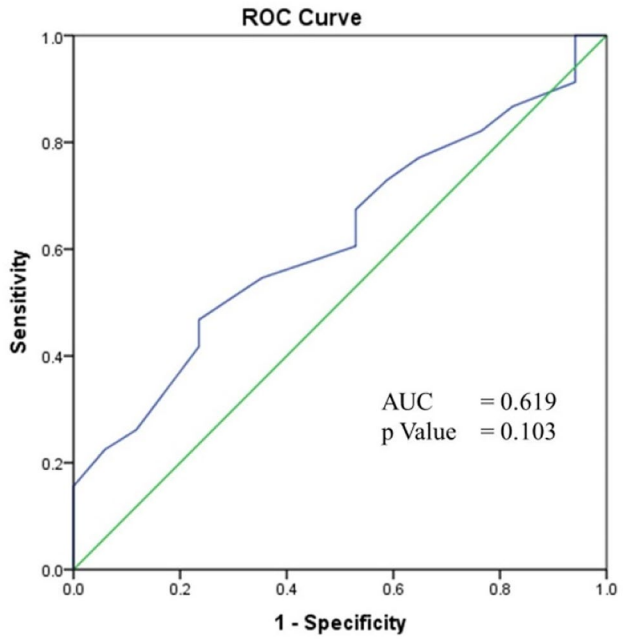

Fig. 2 The diagnostic thresholds of maximal age provided by ROC curve analysis for prediction of clinical pregnancy rate

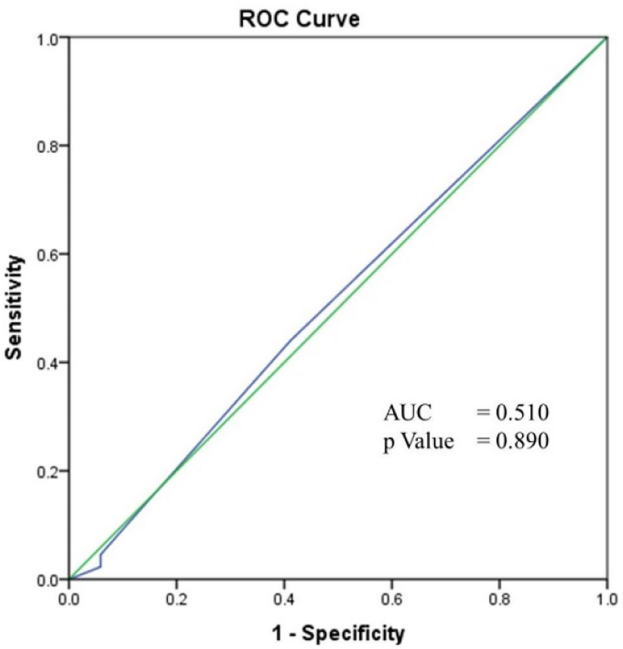

Fig. 3 The diagnostic thresholds of maximal adenomyosis size provided by ROC curve analysis for prediction of clinical pregnancy rate

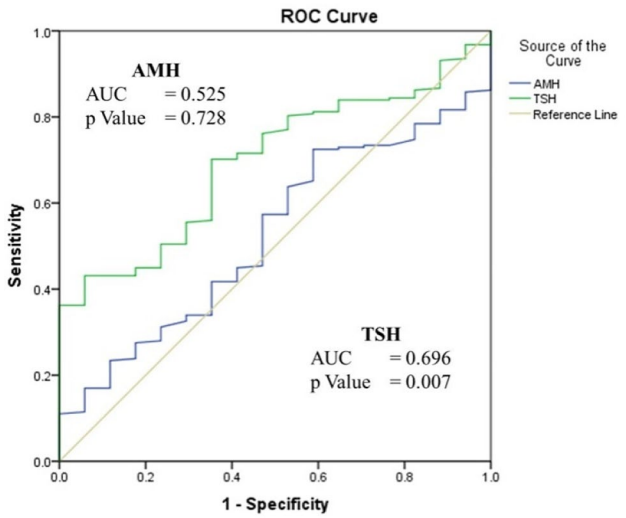

Fig. 4 The diagnostic prediction of AMH and FSH provided by ROC curve analysis for prediction of clinical pregnancy rate

for the retrospective studies remained significant (95% CI 0.402–0.649; CI 0.595–0.796).

Discussion

Adenomysosis is a benign uterine disorder characterized by the presence of ectopic endometrial glands and stroma in the myometrium and reactive hypertrophy and hyperplasia of the myometrium [6].

Various mechanisms have been postulated for the etiogenesis. Tissue injury and repair (TIAR) is the primary mechanism for myometrial invasion. Chronic peristaltic myometrial contraction causes continuous microtrauma to the junctional zone (JZ) causing inflammation leading to increased local estrogens production and a vicious cycle. Prior uterine surgery, cesarean section and repeated endometrial curettage cause tissue damage to the endometrial–myometrial interface supporting TIAR theory. Another theory says the disease arises from metaplasia of embryonic or adult stem cell in myometrium. Chapron et al. in 2017 described the outside to inside invasion theory showing high prevalence of focal posterior adenomyoma in patients with deep infiltrating endometriosis.

TVS represents the first line imaging techniques to diagnose adenomyosis as it is easily available and relatively cost effective with 65% to 81% sensitivity and 65% to 100% specificity. Several criterial-like morphological cervical uterus sonographic assessment (MUSA), Vanden Bosch and de Bruijn et al. criteria [19], Naftalin et al. criteria [16] were available to describe and report the ultra-sonographic features of adenomyosis. The typical features include.

- Asymmetrical thickening of uterine walls.
- Intramyometrial cysts or hyperechoice islands (or both).
- Fan shaped shadowing of the myometrium.
- Irregular or interrupted junctional zone (JZ).
- Myometrial echogenic subendometrial lines and buds.

Magnetic resonance imaging (MRI) diagnosis adenomyosis is based on JZ thickness and the presence of hypointense endometrial glands in myometrium in T2-weighted images. The common appearance of adenomyosis is bulky asymmetric uterus in diffuse adenomyosis thickened JZ (> 12 mm).

Adenomyosis and impact on infertility have been explained by several theories [5]. They include.

- Abnormal uterotubal transport due to anatomical distortion and altered uterine peristalsis.
- Anatomical distortion of the uterine cavity and altered myometrial contractility and loss of normal rhythmic contraction [11].
- Molecular alterations induced by eutopic endometrium causes altered receptivity. This includes altered sex steroid hormone pathway, increased inflammatory mediators (TNF α, IL-1), oxidative stress and reduced implantation markers, lack of adhesion molecules and altered function of HOXA10 gene impair implantation [10].
- *Increased expression of aromatase cytochrome P450* and mRNA leading to conversion of androgens to estrogen in eutopic endometrium leading to increased local estrogen in eutopic endometrium leading to increased local estrogen production.
- Altered expression of estrogen and progesterone receptors, overexpressed IL-6 leads to increased estrogen receptor expression and reduction in progesterone A and B receptors. Progesteron has antiproliferative activity. So, upregulated ER—α receptor reduces β—3 integrin secretion and alters uterine, receptivity.

Among the adhesion molecules, integrinβ-3 and *osteopontin which are a small integrin binding ligand were lower in patients with adenomysis and are associated with impaired implantation*.

- Also, leukemia inhibitory factor (LIF) is much needed cytokine during implantation window which is also reduced in adenomyosis [12, 13].

Sunit Sharma et al. in 2019 [20] showed significant reduction in clinical pregnancy rate, live birth rate and miscarriage rate. Vercellini et al. in 2014 [4] did a metaanalysis of IVF/ICSI outcome in women with adenomyosis and found a 28% reduction in the clinical pregnancy rate.

- Treatment includes GnRH agonist pretreatment, conservative surgery or combined therapy
- GnRH receptors are found in adenomyotic lesions. So, GnRH agonist can have a direct antiproliferative action on the lesions and can reduce the inflammatory reaction

and angiogenesis and can induce apoptosis. Also, it induces hypoestrogenic state as the hypothalamic pituitary ovarian axis gets suppressed and reduces estrogen induced proliferation through estrogen receptors.

Conservative surgery can be done by laparoscopy and two techniques are explained, i.e., the classical adenomyomectomy and the new H-incision technique. The classical technique is done by single incision of uterine wall and stepwise resection of adenomyomatic tissue. In the newer technique, "H" shaped incision is made and adenomyotic tissue is excised, and the wound is closed in 2 layers.

Adenomyosis and impact on pregnancy outcome have been explained by many studies. Increased risk of preterm labor and PPROM has been reported. The pathogenic mechanisms include increased inflammatory mediators, increased myometrial prostaglandins, altered uterine contractility and increased intrauterine pressure. Also, disturbed decidual trophoblast interactions can lead to placenta related disorders including abruption and adherent placenta.

Chiang et al. in 2018 [21] showed association between spontaneous miscarriage rate and adenomyosis in women undergoing IVF cycle and found that spontaneous abortion rate was higher in women with adenomyosis.

Conclusion

In conclusion, our study found that adenomyosis in general has negative impact on ICSI/FET outcome in terms of clinical pregnancy rate. The limitation of the study includes it is a retrospective study and ultrasound is used for the diagnosis. Nevertheless, we found a significant association between GnRH agonist pretreatment, conservative surgery and use of GnRH agonist long protocol in improving the success outcome in ICSI/FET cycle. But further large scale, prospective comparative studies may be beneficial to confirm our result.

Declarations

Conflict of interest The authors declare that they have no conflict of Interest.

Ethical Statement Hereby, I Dr Pradeepa Sudhakar consciously assure that the for the manuscript submitted above where in accordance with the ethical standards and informed consent was obtained from all the patients being included in the study, Prior ethical approval was obtained from the Sudha Hospital Ethical Committee.

Informed Consent Informed consent was obtained from all the patients for being included in the study.

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About the Author

Pradeepa Sudhakar is a Senior ART Consultant at Sudha Hospitals since 2008, Sudha Hospitals has IVF centers at Coimbatore, Salem, Chennai, Madurai, Colombo, Trichy & Hyderabad. She is also holding the post of Vice President. In her career spanning 16 years she has held various posts in Erode OG Society (EOGS) & Erode Chapter of TAPISAR. She was Organizing Secretary for various workshops, conferences and webinars. Presently she is the Joint Secretary in ECOT and was one of the executive members' active in opening this Chapter at Erode. A dedicated IVF specialist who through her hard work has become famous all over South India. She has published many articles, book chapters and posters to her credit and also involved in various research and clinical trials.