Original Article

Live Birth Rates in *In vitro* Fertilization Cycles with Oocytes Containing Smooth Endoplasmic Reticulum Aggregates and Normal Oocytes

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Abstract

Aims: The aims of this study were to compare the live birth, embryological and pregnancy outcomes after intracytoplasmic sperm injection (ICSI) in patients who have oocytes with smooth endoplasmic reticulum aggregates (SERa+ cycles) and patients with normal oocytes and to compare the pregnancy outcomes based on the observed frequency of SERa. **Settings and Design:** The current study was a retrospective case record review of patients undergoing ICSI from 2012 to 2016 in a specialty fertility center. **Materials and Methods:** The patients were divided into two groups based on the presence of SERa: patients with at least one oocyte containing SERa (SERa+ cycles) (n = 112) and patients with normal oocytes (n = 839). The primary outcome measure was live birth rate. The secondary outcome measures were fertilization rate, cleavage rate, blastocyst formation rate, clinical pregnancy rate, miscarriage rate, and anomalies in children born. **Results:** Women with SERa+ cycles showed similar live birth rates, fertilization rates, cleavage rates, blastocyst formation rates, clinical pregnancy rates, miscarriage rates, and abnormalities in children compared to women with normal oocytes. A gradual reduction in live birth rates was observed when the percentage of oocytes containing SERa increased. The group containing >50% of oocytes with SERa demonstrated no live births. **Conclusions:** Presence of SERa had no major overall negative impact on key embryological and live birth outcomes. A reduction in the live birth rate with increasing proportion of SERa oocytes was observed, with no live births in the group with >50% or all affected oocytes.

Keywords: *In vitro fertilization, live birth, oocyte morphology, smooth endoplasmic reticulum aggregates*

Introduction

Human oocytes in assisted reproduction often display morphological intra- and extracytoplasmic abnormalities. The relevance of most of these abnormalities is questionable and uncertain with the probable exception of smooth endoplasmic reticulum aggregates (SERa).[1] SERa were first discovered and reported in 1997[2] and since then their presence has been associated with poorer pregnancy rates, implantation rates, compromised obstetric and neonatal outcomes, and malformations in children born.[3] A case of Beckwith–Wiedemann syndrome (BWS) was reported in a case arising from an apparently normal oocyte in a cohort of oocytes containing SERa.[4] BWS is a disorder caused by modifications in the imprinted gene loci on chromosome 11p15. Affected patients have abdominal wall defects, macrosomia, macroglossia, and predisposition to cancer. In view of these detrimental reports, the Alpha-ESHRE consensus in 2011 recommended to discard oocytes affected with this dysmorphism and to closely examine

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the sibling oocytes.[5] Despite the recommendation, a multicentric survey published in 2015 to understand the change in policy of *in vitro* fertilization (IVF) units toward SERa+ oocytes found that just 14% of the surveyed centers discarded SERa+ oocytes and 43% of centers that did not discard oocytes followed up neonatal data.[6] Over 50% of centers either did not differentiate SERa+ oocytes or transferred SERa oocytes without neonatal follow-up. This study emphasized the fact that greater data monitoring and reporting of SERa+ oocyte outcomes was necessary to modify the current practice.

Oocytes containing SERa show poor fertilization, cleavage, and lower embryo quality. Embryos that originate from oocytes containing SERa have either not been considered for transfer or are considered for transfer only when there are no other suitable embryos and after patient consent. SERa+ cycles are those which contain at least one oocyte with SERa. The sibling oocytes appear to be normal with light microscopy but on electron microscopy have been found to contain subtle, possibly pathological and small SERa.[3] Since these oocytes are utilized, concern remains about their possible impact on the pregnancy outcome.

Several studies have been published evaluating embryological and pregnancy outcome in SERa oocytes and SERa+ cycles. Results published are conflicting, with some studies reporting no significant difference in pregnancy rates[7-13] and some others showing negative effects.[3,13-15] Very few prior studies have reported live birth rate as a primary outcome measure.[8,10,16,17] Moreover, following the 2011 recommendations, there were three publications in 2013 which reported the birth of normal babies originating from oocytes containing SERa.[8,17,18] Discarding oocytes containing SERa increases the risk of cycle cancellation with no embryos available for transfer.[19] There have been prior observations about poor outcomes in women with all or majority of oocytes displaying large SERa, raising speculation about whether a threshold exists between frequency and size of SERa and negative outcomes.[10] There are no published studies evaluating IVF outcome, and SERa frequency. Further data are therefore necessary to understand more deeply the impact of SERa on IVF outcome and whether there exists a subset of patients with poorer prognosis.

In view of the existing lacuna of evidence in the current literature, this study was planned with an aim to (a) compare live birth rates following IVF-intracytoplasmic sperm injection (ICSI) in patients who contain oocytes with SERa (SERa+ cycles) and patients with normal oocytes (SERa− cycles) (b) to compare the fertilization rate, cleavage rate, blastocyst formation rate, clinical pregnancy rate, miscarriage rate and anomalies in children born between the two groups and (c) compare outcomes based on the observed frequency of SERa.

Materials and Methods

Study design and study participants

We have conducted a retrospective record review in a private fertility unit from January 2012 to December 2016. All women undergoing ICSI cycles during the study period who have completed follow-up and where information on the final pregnancy outcome is available were included in the study. Since the presence of SERa cannot be observed on the day of insemination, patients undergoing conventional IVF and split IVF-ICSI were excluded from the study. Patients undergoing surgical sperm retrieval were also excluded. All women with on-going pregnancies at the time of data collection were also excluded from the study.

The participants were divided into two groups based on the presence of SERa. SERa oocytes were defined as those oocytes where one or more SERa were visible with light microscopy after denudation just prior to ICSI. The SERa+ cycles had at least one oocyte with SERa in their oocyte cohort. The SERa− cycles had morphologically normal oocytes.

All the relevant information was retrieved from a retrospective case record review. Apart from the primary and secondary outcome parameters, a list of relevant potential confounders was prepared based on evidence from published literature. Information on all these variables was retrieved from the electronic medical records of the hospital.

Study procedure

All patients underwent the following antagonist protocol. Ovarian stimulation was commenced on day 2 of the cycle using a combination of recombinant follicle-stimulating hormone (Gonal F, Merck-Serono, Geneva, Switzerland; or Recagon, Organon, Oss, The Netherlands) and urinary gonadotropin (Menopur, Ferring Pharmaceuticals, Copenhagen, Denmark). The final trigger was administered when at least >3 follicles were >17 mm. The trigger was either recombinant human chorionic gonadotropin (hCG) (Ovitrelle 250 mcg, Merck-Serono, Geneva, Switzerland) or agonist trigger (triptorelin 0.2 mg, Ferring Pharmaceuticals, Copenhagen, Denmark). Oocyte retrieval was performed 35 h after hCG administration using vaginal ultrasound-guided aspiration of follicles.

Each oocyte was examined at the time of ICSI for the presence of cytoplasmic abnormalities using an inverted

microscope. The day following ICSI, the oocytes were observed for evidence of fertilization and cultured up to blastocyst stage using G1 and G2 media (Vitrolife, Sweden). Embryo morphology was evaluated on days 2, 3, and 5. Embryo transfers were performed on day 3 or 5. A maximum of two embryos were transferred. Embryos originating from SERa oocytes were transferred only when there were no other suitable embryos available for transfer and with patient consent.

Follow-up

All the women who conceived were followed up at monthly intervals as per the hospital protocol. At each followup visit, the progress of pregnancy, vital parameters, and complaints were addressed. They all underwent the first-trimester screening for Down syndrome and an anomaly scan at 20 weeks and screening for gestational diabetes. The final outcome of the pregnancy and live birth was noted for all patients.

Outcome parameters

The primary outcome measure was live birth rate. The secondary outcome measures were fertilization rate (FR), cleavage rate, blastocyst formation rate, clinical pregnancy rate, miscarriage rate, and anomalies in children born. The FR was defined as the ratio between the number of fertilized oocytes and the total number of metaphase II (MII) oocytes injected. Cleavage rate was the ratio between the number of cleaved embryos to total number fertilized. Blastocyst formation rate was defined as the ratio between total number of good quality blastocysts formed and total embryos cleaved. Clinical pregnancy rate was defined as pregnancies with at least one gestational sac divided by a number of embryo transfers. Live birth rate was defined as the ratio between number of patients with live-born babies and number of embryo transfers performed.

Embryos derived from SERa oocytes were not preferred for transfer. They were utilized only when there were no other embryos suitable for transfer and with patient consent. Patients were stratified into three groups based on the proportion of oocytes affected with SERa (Group 1 with <30% SERa oocytes; Group 2 – 30%–50%; and Group 3 – >50% of oocytes with SERa). The outcomes in these three groups were compared as above.

This study was approved by the Institutional Review Board and Ethical Committee.

Statistical analysis

Live birth rate was the primary end-point. The entire dataset was analyzed for the proportion of the missing values. None of the variables included in the final analysis had missing values.

All the quantitative variables were assessed for a normal distribution within each cohort by visual inspection of histograms, skewness, and kurtosis *Z*-values and Shapiro–Wilk test *P* values. All the quantitative baseline parameters/potential confounders were compared between two groups using Independent sample *t*-test/Mann–Whitney U-test depending on their distribution. The categorical variables were compared using Chi-square test/Fisher's exact test.

The key outcome parameters were compared between the two groups using Chi-square test. $P < 0.05$ was considered statistically significant.

Results

A total of 2044 women were screened for eligibility, and of which, 1093 were excluded due to various reasons [Figure 1]. A total of 951 cycles were included in the final analysis. Of these, 112 cycles showed the presence of SERa; making the prevalence of SERa 11.7% in our patient cohort. The remaining 839 cycles had morphologically normal oocytes. All the women had completed their follow-up and the final outcome data were available [Figure 1].

The median age was 31 and 32 years, respectively, in SERa+ cycles and SERa− cycles. No statistically significant differences were observed between both the groups in terms of the days of stimulation, number of oocytes retrieved and number of MII oocytes. In both the study groups, major proportion of embryo transfers were done either on day 3 or 5, with a minor proportion of women receiving embryo transfer on day 4. There was no statistically significant difference in the proportion of embryos transferred on different days. Embryo transfer was done on day 3 when the couple did not consent for blastocyst transfer or when there were only two embryos available for transfer. The number of good quality embryos available for transfer and freezing and number of embryos transferred were also comparable between two groups. The most common trigger used was recombinant hCG in both the groups, followed by highly purified hCG. A minor proportion of women in both the groups received gonadotropin-releasing hormone agonist or dual trigger. There was a statistically significant difference in the type of trigger administered (the agonist and dual trigger) between SERa+ and SERa– cycles. However, considering the small proportion of patients in the dual trigger group, this difference is least likely to have any major impact on outcomes [Table 1].

The FR, cleavage rate, and blastocyst formation rate were comparable between both the groups. The clinical pregnancy rate was 41.1% and 37.7%, respectively, in SERa+ and SERa– cycle groups ($P = 0.48$). The

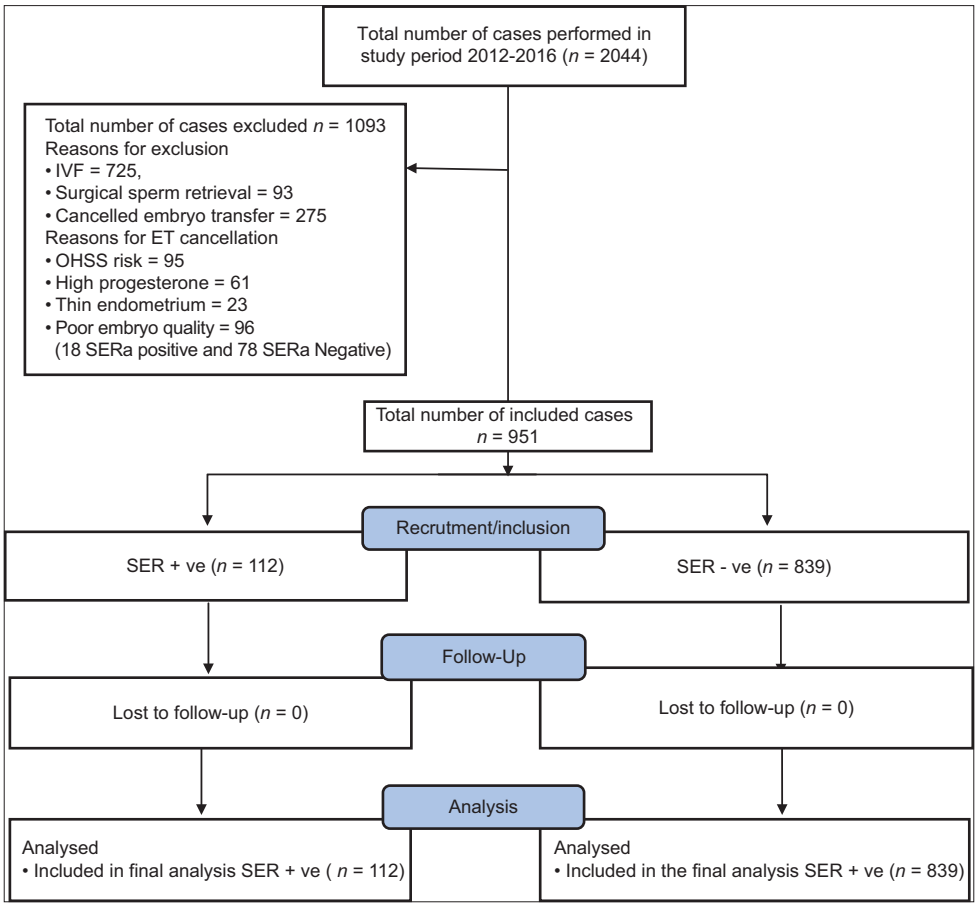

Figure 1: Flow chart of the study participants

miscarriage rate was 6.3% and 7.2%, respectively, in SERa+ and negative groups (P = 0.726). The live birth rate was 33.9% in SERa+ cycle group and 28.5% in SERa– cycle group (P = 0.233). There was no statistically significant difference in any primary or secondary outcome parameter between both study groups [Table 2]. There were two patients with fetal abnormalities detected on anomaly scan (both cardiac abnormalities-single ventricle; complex multiple aortic abnormalities) in the SERa absent group and none in the SERa+ group. Both the patients with anomalous fetuses opted for termination of pregnancy.

SERa+ cycles were stratified into three groups based on the percentage of oocytes containing SERa – Group 1 had <30% of oocytes with SERa, Group 2 had 30%–50% oocytes with SERa, and Group 3 had >50% of oocytes with SERa. Fertilization rates, cleavage rates, pregnancy rates, and live birth rates were calculated for these three groups [Table 3]. The three groups were comparable with respect to age of the woman, number of MII oocytes retrieved, day of embryo transfer, and number of embryos transferred per patient. The fertilization and cleavage rates were similar in all three groups. The number of top quality embryos available for transfer reduced as the frequency of SERa increased. Table 3 indicates an inverse relationship between % of SERa+ oocytes and live birth rates. The pregnancy rates were 51.92%, 31.81%, and 14.3% in Group 1, 2, and 3, respectively (P = 0.075). The live birth rates were 44.23%, 27.27%, and 0% in the three groups, respectively. There were no live births in the group with >50% SERa oocytes. This indicates that the presence of greater number of SERa oocytes in the cohort may not affect fertilization and cleavage rates but may cause a significant decline in the pregnancy and live birth rates, especially when >50% of oocytes demonstrate SERa. This can be a poor prognostic indicator in IVF [Table 3]. These observations of reduction in live birth rate did not reach statistical significance probably due tothe small sample size of the patients.

Discussion

The results of our retrospective cohort study highlight that women with SERa+ cycles showed similar live birth rates compared to women with SERa− cycles. There was no significant difference in FRs, cleavage rates, blastocyst formation rates, clinical pregnancy rates, or

Table 1: Comparison of population characteristics between smooth endoplasmic reticulum aggregate+ and smooth endoplasmic reticulum aggregate− cycles (*n*=951)

Baseline characteristics	SER status		*P*
	SERa+ cycles (*n*=112)	SER−cycles (*n*=839)	
Age of woman, median (IQR)	31 (29 -34)	32 (29 -35)	0.112
Days of stimulation, median (IQR)	9 (9 -11)	10 (9 -11)	0.203
Number of oocytes retrieved, mean±SD	10.33±4.79	11.48±6.28	0.062
Number of MII oocytes, mean±SD	7.71±3.95	8.54±5.05	0.094
Day of transfer			
2nd or 3rd day	52 (46.4)	373 (44.5)	0.912
4th day	8 (7.1)	66 (7.9)	
5th	52 (46.4)	400 (47.7)	
Number of good quality embryos available for transfer and freezing, mean±SD	3.33±2.14	3.46±2.48	0.611
Number of embryos transferred, mean±SD	1.85±0.63	1.82±0.6	0.600
Trigger type, *n* (%)			
Recombinant hcG	71 (63.4)	468 (55.8)	0.126
hcG hp	29 (25.9)	222 (26.5)	0.902
GnRH agonist trigger	9 (8.0)	145 (17.3)	0.012
Dual trigger	3 (3.488)	4 (0.574)	0.011

GnRH=Gonadotropin-releasing hormone, hcG=Human chorionic gonadotropin, hp=Highly purified, IQR=Interquartile range, SER=Smooth endoplasmic reticulum, SERa=SER aggregate, MII=Metaphase II, SD=Standard deviation

Table 2: Comparison of live birth rate and secondary outcome parameters between smooth endoplasmic reticulum aggregate+ cycles and smooth endoplasmic reticulum aggregate− cycles (*n*=951)

Parameter	SERa+ cycles (*n*=112), *n* (%)	SERa− cycles (*n*=839), *n* (%)	*P*
Fertilization rate	713/863 (82.61)	6069/7163 (84.72)	0.096
Cleavage rate	663/713 (92.98)	5547/6069 (91.39)	0.148
Blastocyst formation rate	246/713 (34.50)	2222/6069 (36.61)	0.267
Clinical pregnancy rate	46/112 (41.1)	316/839 (37.7)	0.485
Miscarriage rate	8/112 (7.1)	59/839 (7.0)	0.966
Live birth rate	37/112 (33.9)	240/839 (28.5)	0.332
Fetal abnormalities	0	2*	

*Both were cardiac abnormalities (single ventricle; complex aortic abnormalities) detected at NT scan. SERa=Smooth endoplasmic reticulum aggregate, NT=Nuchal translucency

miscarriage rates between the two groups. There was no increase in the rate of abnormalities in children born in the SERa+ cycles. A gradual reduction in live birth rates was observed when the percentage of oocytes containing SERa increased. The group containing >50% of oocytes with SERa demonstrated no live births, and this could be a marker for poor prognosis in IVF cycles. The prevalence of SERa in IVF cycles was found to be 11.7% which is in comparison with what is reported in the literature (10%).[20]

SERa in oocytes were first discovered by Serhal *et al*.[2] in 1997 and were observed to be associated with lower fertilization, cleavage, clinical pregnancy, and implantation rates. The presence of SERa may be due to ovarian hyperstimulation in view of their increased frequency in women receiving higher gonadotropin doses and longer stimulation.[17] Their prevalence in a natural cycle or mild stimulation IVF is not reported. Smooth endoplasmic reticulum and mitochondria act as calcium stores necessary for fertilization and early embryo development. Presence of large SERa is known to disturb the Ca^2 + stores and oscillations and resultant reduced fertilization and cleavage rates.[20,21] The data in existing literature about the impact of SERa oocyte or SERa+ cycles on fertilization, clinical pregnancy, live birth, and neonatal outcome are conflicting. Ten studies have reported the impact of the above outcome measures in SERa oocytes. Just one[13] of the ten studies reported show a significant decline in FR in affected oocytes. The remaining nine studies showed comparable FRs in normal oocytes and SERa oocytes.[7-10,12,14-17] Eight studies have reported clinical pregnancy as an outcome[7-10,14-17] and four have reported live birth rate.[10,8,16,17] Of the eight studies, all studies have a lower pregnancy rate in SERa oocytes, but only in one study, the difference reached statistical significance.[15] There was no difference in the live birth rate reported in the four studies between SERa oocytes and normal oocytes.[10,8,17,16]

Table 3: Cycle characteristics and Live birth rate based on frequency of smooth endoplasmic reticulum aggregate oocytes

Frequency of SER[a]	<30%	31-50%	51-100%	100%+	*P*
Number of cases	52	22	7	4	
Average Age (years)	32	34.13	31.71	30.25	0.149
Number of M II oocytes per cycle (no of MII oocytes/total number of cycles)	12.88 (675/52)	11.63 (256/22)	10.14 (71/7)	8.75 (35/4)	0.796
Fertilisation rate	82.02%	86.38%	83.92%	85.71%	0.899
Cleavage rate	91.7%	98.18%	100%	100%	*
Day of transfer					
Day 3	23	11	3	1	0.891
Day 5	29	11	4	3	
Number of embryos transferred/pt@	1.71 (89/52)	1.54 (34/22)	1.42 (10/7)	1.5 (6/4)	0.833
Total number of good quality embryos available for transfer & freezing per patient	4.46 (232/52)	2.77 (61/22)	2.57 (18/7)	2.5 (10/4)	0.791
Quality of embryos transferred					
Group A1	57.69% (30/52)	50% (11/22)	28.57%(2/7)	25% (1/4)	*
Group B2	34.61 (18/52)	45.45% (10/22)	71.42% (5/7)	75% (3/4)	
Group C3	7.69 (4/52)	4.55% (1/22)	0	0	
Clinical pregnancy rate	51.92%	31.81%	14.3%	0	0.075
Live birth rate	44.23%	27.27%	0	0	*

Our data have not shown any difference in fertilization, clinical pregnancy, and live birth rates between SERa+ cycles and SERa– cycles. This is similar to most of the results of earlier studies. Eight studies have reported FRs[3,8-11,14,17,16] with only one study[14] reporting a significant reduction in FRs in SERa+ cycles. A reduced clinical pregnancy rate was observed in one study[3] and the remaining seven studies observed no difference. Live birth rate in SERa+ cycles has been published in four studies and none show any significant difference; which concurs with our findings too.[10,16,8,17]

There were prior observations about poor outcomes in women with all or majority of oocytes displaying large SERa, raising speculation about whether a threshold exists between frequency and size of SERa and negative outcomes. Munaswamy *et al*. in 2008 compared the effect on pregnancy rates with varying proportion of SERa in each cohort and found no significant difference in pregnancy outcome irrespective of the proportion of SERa. None of the prior studies have attempted to analyze factors that predispose to higher frequency SERa+ oocytes or size of SERa. We had seven patients with >50% oocytes affected for whom no live births occurred. Four patients had all affected oocytes and no live births. However, due to smaller sample size of the patients in each group and higher probability of chance, no valid conclusions can be made regarding this trend. The phenomenon needs to be tested by further large scale studies. This information would assist in the stratification of outcome based on prognosis. Published data about patients with all affected oocytes shows that though some live births have been reported, many do exhibit poor outcome.[8,11,20,22,23]

Published data show over 200 healthy live births originating from SERa+ cycles and 22 healthy babies from SERa+ oocytes.[20] Deselection of embryos originating from affected oocytes increases cycle cancellation rates, rejects possible usable embryos destined to result in live births and precludes a couple from an opportunity to have their own genetic child.[19] It is important to reach some consensus about the impact of SERa oocytes on pregnancy and neonatal outcome, and in light of the current data, a probable modification of the current guidelines may be necessary.

The main strength of the study is that live birth rate is the primary outcome measure. Stratification of cases based on SERa+ oocyte percentage and outcome comparisons are also novel and not previously analyzed. The limitations of the study are that it is a retrospective cohort study. We could also not calculate SERa oocyte outcome data since single embryo transfer was not universally performed and a greater number of patients received double embryo transfer. Finally, the group that contained >50% SERa oocytes was small.

The lack of statistical associations may be attributable to the inadequate power of the study and hence the role of chance cannot be ruled out. Even though multiple clinicians were involved, all the study procedures and assessments were conducted as per the standardized protocol of the institution and hence the probability of bias attributable to misclassification and ascertainment is

minimal. Since there were no losses to follow-up in either of the study groups, there was no possibility of bias due to differential loss to follow-up. The role of confounding factors could not be assessed due to inadequate sample size. The study results can be generalized to similar settings, where similar management protocols are being followed.

Conclusions

Data regarding clinical outcomes in SERa+ cycles are few and conflicting. It appears that cycles containing a low frequency of affected oocytes in the cohort have similar fertilization, cleavage, clinical pregnancy, and live births as their normal counterparts. We observed a significant reduction in live birth rates with increasing proportion of SERa oocytes and no live births in the group with > 50% or all affected oocytes. The difference did not reach statistical significance probably in view of low sample size. Larger studies are necessary to confirm the current observation. Since many live births are being reported from affected oocytes, the strength of association between SERa and abnormalities in children born is unclear.

Outcome data from embryos originating from SERa oocytes must be published. Larger studies with details of frequency and size of SERa and outcome are necessary to add to the existing evidence. It may be interesting to observe whether the proportion and size of SERa have any correlation with total gonadotropin dose, estradiol levels on hCG day and duration of stimulation.

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Conflicts of interest

There are no conflicts of interest.

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