Embryo apoptosis may be a significant contributing factor in addition to aneuploidy inhibiting live deliveries once a woman reaches age 45

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Summary

Purpose: To determine the relative role of aneuploidy vs embryo apoptosis as the etiologic factor of poor pregnancy rates with advancing age. *Materials and Methods:* A retrospective review of chemical vs clinical vs live delivery pregnancy rates in women aged 40-42, 43-45, and ≥ 45 years is reported. The data were further stratified according to oocyte reserve based on day 3 serum follicle-stimulating hormone (FSH) ≤ 11 mIU/ml vs >12 mIU/ml. *Results:* For women aged 40-42 years there were no differences in live delivery pregnancy rates in women with normal vs decreased egg reserve (DOR). There were no differences in live delivery pregnancy rates in women aged 40-42 years vs 43-44 years with normal oocyte reserve; however despite no differences in clinical pregnancy rates in women aged 43-44 years with normal vs DOR, the live delivery pregnancy rates were markedly lower in the group with DOR. In contrast, there were very low chemical pregnancy rates in women aged ≥ 45 years. *Conclusions:* As seen in younger women, there does not appear to be any increased risk of meiosis errors in women aged 40-42 years with DOR compared to women of the same age with normal reserve. Low pregnancy rates in women aged 43-44 years with DOR is related to meiosis errors. In contrast the very low chemical pregnancy rates found in women aged ≥ 45 years despite embryo transfer (ET) suggest embryo apoptosis is mostly responsible for poor pregnancy rates in this very advanced reproductive age group.

Key words: Apoptosis; Meiosis errors; Reproductive aging; In vitro fertilization; Pregnancy rates.

Introduction

Poor pregnancy rates with advanced reproductive age is predominately related to a strong tendency for meiosis I and meiosis II errors; however there may be a contribution of a tendency for embryo apoptosis.

The objective of this study was to determine the relative contribution of aneuploidy vs embryo apoptosis on failure to achieve a live delivery in women of advanced reproductive age following in vitro fertilization-embryo transfer (IVF-ET). Furthermore, the study would determine the confounding effect of adequate vs diminished oocyte reserve (DOR) in women ≥ 40 years of age.

Materials and Methods

Women undergoing IVF-ET aged ≥ 40 years were divided into four age ranges: 40-42, 43-44, 45-46, and 47-49. They were further stratified according to normal day 3 serum follicle-stimulating hormone (FSH) of ≤ 11 mIU/ml vs elevated at ≥ 12.

The authors assumed that the difference between a + beta (β) human chorionic gonadotropin (hCG) level (≥ 100 mIU/ml with two consecutive rises) vs live delivery rate (DR) was attributed to pregnancy loss from aneuploidy but failure to establish a β-hCG was related to early embryo apoptosis. A clinical pregnancy was defined as ultrasound evidence of pregnancy at eight weeks, and a viable pregnancy as a live fetus at 12 weeks.

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Results

The pregnancy rates according to age and day 3 serum FSH in women of advanced reproductive age are shown in Table 1. Combining both FSH groups, 31.5% of ETs in women aged 40-42 years resulted in a + β-hCG vs 36.0% for women aged 43-44 years vs 6.8% for women aged 45-49 years ($p < 0.0001$ comparing women aged 40-44 years vs ≥ 45 years, Fisher's exact test).

The live DR was 16.3% for women aged 40-42 years vs 11.3% for women aged 43-44 years vs 1.7% for ages 45-49 years ($p < 0.0001$ Fisher's exact test). Though the clinical pregnancy rates per transfer were almost identical in women aged 43-44 years with normal vs DOR, there was a large difference in the live DR per transfer (p = 0.0178, Fisher's exact test).

Discussion

DOR did not effect the live DR in women aged 40-42 years. However, women aged 43-44 years with oocyte depletion had a much lower chance of a live delivery, mostly related to aneuploidy as evidenced by similar clinical pregnancy rates per transfers to those women aged 43-44 years with normal day 3 serum FSH.

For women aged ≥ 45 years the very low rate of attaining a positive beta hCG level suggests that embryo apoptosis was highly prevalent in this group. These data

Table 1. — *Pregnancy rates (PRs) according to age and day 3 serum FSH in women of advanced reproductive age.*

Age at time of retrieval (years)	40-42		43-44		45-46		47-49
Baseline FSH levels	≤ 11	≥ 12	≤ 11	≥ 12	≤ 11	≥ 12	All serum FSH
# transfers	737	198	121	73	77	61	37
% w / positive β-hCG	29.9	43.4	33.9	39.7	5.2	9.8	5.4
Clinical PR (%) / transfer	23.9	32.8	26.4	26.0	3.9	6.6	0.0
Viable PR (%) / transfer	18.5	21.7	21.5	6.8	1.3	4.9	0.0
Live DR (%) / transfer	15.6	19.2	15.7	4.1	1.3	3.3	0.0

support previous conclusions that oocytes from younger women with DOR are not of similar quality to women of older age with similar degree of oocyte depletion, but have a quality more similar to their age peers [1-3].

Although women with normal oocyte reserve are less likely at age 40-42 years to have a successful pregnancy related to an increased risk of aneuploidy compared to younger women with normal oocyte reserve, women in this age group with DOR are not more prone to meiosis errors compared to their age peers with normal reserve as evidenced by similar live DR. The data from the 40-42 year old group supports the contention that the very low pregnancy rates reported by many other studies of IVF in women with elevated day 3 FSH may be related to the use of the high-dosage gonadotropins leading to embryos that appear normal but do not implant [4, 5].

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