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Reproduction in older women

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SPONTANEOUS REPRODUCTIVE PERFORMANCE IN OLDER WOMEN

Leridon[1] (1977) and later Stein[2] (1985) have shown that fecundity appeared to be decreasing with time, from 17th century to the present era irrespective of the women's age. However, irrespective of the different centuries, women's fecundity started to decrease after 25 years of age but the decrease is more exaggerated after 34 years of age, and was approaching zero after 45 years of age.

While everyone agrees the reproductive performance decreases with ageing, there is no consensus at what age the fertility starts to decline. James[3] (1979) suggested the start of decline was 20 years of age; while other[4] suggested significant decline in fertility occurred after 30 years of age (eg. the pregnancy rate of 73% for those aged 30 or less, 61% for those aged 31 to 35 and 54% for those aged 35 or more). A review has been provided by Gindoff and Jewelewice[5].

POSSIBLE CAUSES OF DECLINED FERTILITY IN OLDER WOMEN

1. DECREASED OVULATION

Lenton et al (1984)[6] suggested endocrinological changes (eg. increased plasma FSH and decreased oestradiol) may start 5 to 10 years before menopause. This may be due to decreased hypothalamo-pituitary response to plasma oestradiol suppression with increasing age. Another possible cause is related to decreased plasma inhibin level. Under both circumstances, it is possible to have raised plasma FSH but normal plasma oestradiol level. Only after the actual depletion of follicles will the plasma oestradiol level decrease clinically. Before this occurs, the woman may possibly have an irregularity and shortening of cycles (eg. follicular phase averages 14.2 days in these ladies aged 18 to 24 while it becomes 10.4 days in those aged 40-44). Jones and Jones (1986)[7] had made similar observation in those going through IVF cycles. However, although birth rate decreased by half in those aged 40 to 44 compared to those aged 35 to 39, only 16 to 30% of the menstrual cycles were found to be abnormal. Therefore changes in the hypothalamo-pituitary ovarian axis only explained some of the cases. Treloar et al (1967)[8] also showed years before menopause, there was increased variability in intermenstrual intervals. There may be a small yet steady decreased cycle length due to shortened follicular phase. Sherman et al (1975)[9] showed there was no significant endocrinological change in women aged 40 and 41 with regular menses compared to those aged 18 to 30. However, in those over 45 years of age, there was a significant difference.

2. POOR OOCYTE QUALITY

Fujino et al (1996)[10] reported that when compared with the oocytes from the younger female mice, those oocytes from the aged female mice showed increased DNA fragmentation which may represent apoptosis. The fertilisation rates of the oocytes from the aged mice were also lower. Navot et al (1991)[11] also suggested poor oocyte quality rather than implantation failure as the cause of declining fertility in older women. About 25% of the unfertilised oocytes in IVF patients from our centre were reported to have chromosomal abnormality (Bongso et al 1988)[12]. However, it is still controversial if this is age-related. Plachot et al (1988)[13] found significantly increased aneuploidy with increasing age, but this was not confirmed by others (Lim et al 1995)[14].

3. IMPAIRED FERTILISATION

The belief that decreased fertilisation with age has never been confirmed. Lim & Tsakok[15] (1997) showed no statistically significant difference in the fertilisation rates with age in the IVF cycles. The fertilisation rates were 50.9% for those aged < 34 years, 49.3% for aged 35 to 39 years and 37.9% for aged ≥ 40 years, though the pregnancy rates were significantly lower in those ≥ 40 years (14.3%) compared to those < 34 years of age (43.2%). Padilla and Garcia[16] (1989) had shown no significant difference in the embryo transfer per oocyte retrieval with age, they were 89% for those aged < 30, 85% for aged 30-34 and 78% for

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women aged ≥ 40 years. Similar views were also shared by other authors (Romeu et al 1987[17], Oehringer et al 1995[18])

4. IMPAIRED UTERINE RECEPTIVITY

This long time belief that reduced uterine receptivity[19,20] may be responsible for the lower fertility in older women is being challenged. Navot et al[11] (1991) showed in a group of infertile women aged ≥ 40 years, oocyte donation with IVF gave significantly higher pregnancy and delivery rates (56% and 30%) respectively compared to using their own oocytes (5.3% and 0% respectively with induction of ovulation; 3.3% and 0% respectively with IVF). Furthermore, when the IVF pregnancy outcomes of a group of oocyte donors and their recipients were compared, there was no difference in the pregnancy (33% vs 40% respectively) or delivery (23% vs 30%) respectively. All these suggested that uterine factor is relatively unimportant provided good quality oocytes were used. Navot's view was supported by other reports[18,19].

5. INCREASED MISCARRIAGE

Many reports have demonstrated an increase of miscarriage rate associated with increasing age, irrespective of previous obstetric history[21-25]. Warburton et al[26] (1986) showed that 9.9 to 11.7% miscarriage rate in women aged 15 to 34. After 34 years of age, the miscarriage rates progressively increased to 17.7% for those aged 35 to 39, 33.8% for aged 40 to 44 and 53.2% for those aged ≥ 45 years.

The trend is similar with IVF, Padilla and Garcia[16] (1989) showed miscarriage rates of 22% in those aged ≤ 30 years, 32% in those aged 30 to 34 years, 29% in those aged 35 to 39 years but markedly increased to 50% in women aged ≥ 40 years.

The increased miscarriage rates after 34 years of age may be explained by the increased cytogenetic abnormalities (especially trisomies) with age (Wright[27], 1976). This trend appears to be similar to the increased livebirths of Down's syndrome after 34 years of age. Warburton[26] (1986) showed 0.79 to 0.90% trisomy 21 among abortions between ages 15 and 29 years. The rate increased to around 2% between ages 30 and 39 years, 9.26% between ages 40 and 44 years and 28.57% for those aged ≥ 45 years. Similarly, trisomic livebirth rate was 0.06 to 0.09% between ages 15 and 29 years, 0.15% between ages 30 and 34 years. 0.37% between 35 and 39 years of age 1.5% between ages 40 and 44 years and 6.2% for those ≥ 45 years. The rate of trisomy 21 in abortions was 0.53 to 0.65% between ages 15 and 39 years increased to 0.76% between ages 40 and 44 years and 0.84% for those ≥ 45 years.

6. ASSOCIATED MALE FACTOR

It is expected that the husbands of the older women are usually even older. Anderson[28] (1975) showed, from Irish census data that there was a decline in infertility in men older than 57.5 years of age. However, it is less likely this had an important impact as the usual discrepancy of the ages between the couples is not as great.

CAN ART HELP TO REVERT THE DECLINE IN FERTILITY IN THE OLDER WOMEN?

Padilla and Garcia[16] (1989) analysed in a 3 year period, the IVF results of 512 women undergoing 1101 oocyte retrievals (119 for those <30 years, 435 for women aged 30 to 34 years, 436 for those 35 to 39 years and 111 for women ≥ 40 years). An average of 84% had embryo transfer (89% for ages < 30 years, 85% for ages 30 to 34 years, 84% for ages 35 to 39 years and 78% for ages ≥ 30 to 34 years, about 20% for women ≥ 35 years). The clinical pregnancy rates per embryo transfer showed similar trend (34% for < 30 years, 29% for 30 to 34 years, 23% for 34 to 39 years and 25% for those ≥ 40 years). At the same time, abortion rates increased drastically for women ≥ 40 years (50% compared to 22 to 32% in the other age groups). Using the simple linear regression analysis, there appeared a constant decline in the ongoing pregnancy rate per transfer with age.

Penzias et al[29] (1991) reported the use of GIFT in 59 women aged 40 to 47 years undergoing 12 GIFT cycles in 18 months. The results were compared with those <40 years of age undergoing GIFT during the same period under the same protocol. Only 73 (59.8%) ended in gamete transfers with 7 (5.7%) clinical pregnancies and only 5 (4.1%) deliveries. When GIFT results were analysed according to 3 age groups (Group A aged ≤ 34 years, Group B aged 35 to 39 years, Group C aged ≥ 40 years), there was significantly lower pregnancy/transfer rate in group C (9.5% compared to 29.4% in group A and 25.0% in group B).

Bopp et al[30] (1995) reported a bigger series of IVF (2931 cycles) and GIFT (1826 cycles) results. In both IVF and GIFT, significantly higher cancellation rates were observed in women aged 40 to 43 years (49.5% and 25% respectively) and

44 to 45 years (69.5% and 31% respectively) when compared to those 25 to 39 years of age (38.3% and 15.1% respectively). No delivery was noted in those women aged 44 to 45 years. In IVF, the delivery rates per stimulation and per transfer were significant lower in those aged 40 to 43 years compared to younger women (5.4% and 10.8% compared to 8.9% and 14.4% respectively). The discrepancies in GIFT were even bigger. The delivery rates per stimulation and per transfer were 9.2% and 12.2% in those aged 40 to 43 when compared to 21.5% and 25.4% respectively in those 39 years of age or younger.

Using Life Table Analysis, Tan et al[31] (1992) reviewed the results of 5055 consecutive IVF cycles in 2735 patients resulting in 773 clinical pregnancies and 518 live births. It was shown that both cumulative pregnancy and livebirth rates were statistically significantly lower in women aged 35 years or above. The cumulative pregnancy rates were 54% for those aged 20 to 34 years, 39% for those aged 35 to 39, and 20% for those aged 40 years or above. The cumulative live birth rates were 45%, 29% and 14% respectively for the 3 groups. The pregnancy failures were between 27.3% and 29.8% for those aged 20 to 34 years. But it was significantly increased to 40.5% in those 35 years of age or older. The age specific probabilities of conception and livebirth both were calculated to drop with increased treatment cycle especially after the 5th cycle. These effects were even more marked in those aged 35 years and above.

Lim and Tsakok[15] (1997) reported the IVF/ICSI results in the 3 age groups (group 1, aged 34 or less; group 2, aged 35 to 39 years, group 3, aged 40 years or above) in a total of 151 patients undergoing 158 IVF/ICSI treatment cycles. There were no differences in the fertilisation rates in the 3 groups (37.9 to 50.9%). However, pregnancy rates were significantly lower in group 3 (14.3%) and group 2 (32.7%) when compared to group 1 (43.2%)

In conclusion, IVF, GIFT or ICSI all cannot revert to the decrease of fertility rates after 34 years of age. The concept may be extended to suggest that the chance of conception through ART are extremely remote at 45 years of age or above. Furthermore, if an arbituary figure is to be suggested, most women undergoing ART treatments, should be well counselled carefully with regards to further attempt after failing 5 treatment cycles, especially for women aged 35 or above. It is advisable, if ART is likely the treatment of choice, it should be commenced as soon as possible in women aged 30 years or older.

HOW CAN MEDICAL TECHNOLOGIES HELP TO MINIMISE THE ADVERSE EFFECT OF AGE ON FERTILITY?

Various attempts have been employed especially in relation to induction of ovulation and ART in an attempt to improve the reproductive performances of the older women.

STIMULATION REGIME

Rozenwaks et al[31] (1995) tried to increase the dose of gonadotrophin in women with high baseline FSH undergoing IVF treatments but results were not promising. Jinno et al[32] (1996) proposed in a small study, the use of pulsatile gonadotrophins in 88 patients who failed previous in vitro fertilization to improve the embryo quality and pregnancy rates (30% compared to 11% in controm). But there was no statistical difference in livebirth rates (20% compared to 9% in control). This approach is not widely practised.

There are three ways to improve the fertility rates in the older women.

1. Super ovulation with the aim of increasing the number of embryos to be replaced

2. Assisted Hatching

3. Oocyte Donation

1. SUPEROVULATION AND INCREASED NUMBER OF EMBRYOS REPLACED

Hull et al[34] (1996), after controlling other factors e.g. stimulation regimes, numbers of embryos replaced, showed there was no age-related differences in the fertilisation rates or embryo cleavage rates in the older women. However, there was decreased implantation and livebirth rates per transfer in women aged 40 to 44 years when compared to those in younger women (6.7% compared to 14.4 to 17.9% pregnancy per transfer (8.8% compared to 27 to 32% livebirth per transfer). Therefore it was proposed the transfer of higher number of embryos may partially compensate.

This was supported by Widra et al[35] (1996) when 4 or more embryos were replaced in women aged over 40 years, the results became comparable to those of the younger women.

However, this is against the trend of reproductive medicine when hyperstimulation and its associated complications are the main concerns. In fact, many

centres with good results are decreasing the number of embryos replaced, or changing to a less aggressive stimulation regime, to the extent that unifollicular or bifollicular developments are the objectives.

2. ASSISTED HATCHING

One of the possibility for decreased implantation may be due to abnormality in the zona pellucida. Therefore various ways of making a breach in the zona may assist the hatching of blastocyst and effect the implantation. For example, zona can be dissected mechanically[36], "drilled" with acidic Tyrode solution[37] or laser[38-40], zona "rubbing"[41] and zona "thinning"[42]. Schoolcraft et al[43] (1995) reported in a retrospective analysis of 23 cycles, increased implantation rate (22%) with assisted hatching in women 40 years of age or above (compared to 6% in control). Similarly, the viable pregnancy rate was also increased to 48% (compared to 11% in control). Stein et al[44] (1995) showed that in those women over 38 years of age with recurrent implantation failure after IVF, the assisted hatching (using partial dissection technique to create a slit in the zona) increased the pregnancy rate to 24% (compared to 7% in the controls).

Wiemer[45] (1996) combined the use of co-culture and assisted hatching. In women aged 40 or above, the pregnancy rate of women was increased to 30% and this was similar to the rate in women aged 39 or less (41%).

However, just like any new technologies, non selective use of assisted hatching may not show the desirable benefits[46]. Besides, the patients should be informed the possible risk of damage to the oocytes, or obstetric complication (e.g. pre-eclampsia, monozygotic or conjoined twins). The value of this technique needs more experience to prove or disprove. Most likely, assisted hatching should be provided for some selected groups of patients, e.g. older women, repeated IVF or implantation failures, or raised baseline FSH.

Recently, our centre[47] has published zona free blastocyst transfer pregnancy which may offer another option for the old women.

3. OOCYTE DONATION

As discussed earlier, several reports[11,22,23] had showed the pregnancy rates in an old recipients were the same as those in the young donors. Other reports had confirmed similar findings. These suggest the age effect of the woman on reproductive performance can be reverted if the good quality oocytes are donated from the young fertile donors.

CONCLUSION

The effect of age on the reproduction of older women is well known. Despite controversy with regards to the exact time of decline, it seems the effect is a continuous one and is more marked at or after 34 years of age. At or after this age, even ART does not help to revert this trend. Therefore, it is advisable for infertile women to receive specialist attention immediately if she is 30 years of age or above. If ART is the likely choice of treatment, the woman should be advised not to delay receiving the ART treatment. For the national interest, health insurance companies should be negotiated to give special coverage for women in this age group to increase the cost-benefit of the ART treatment (e.g. shorten the waiting period before the policy is effective).

Again there is no consensus to the upper age limit of the ART (excluding oocyte donation). As it is extremely remote to get a viable pregnancy from ART beyond the age of 45 years, it may be reasonable to propose this as the upper limit. But all women undergoing ART at or after 35 years should be cautioned the lower chance of conception so that they would not be misled by the "average" success rates of the centre. More serious cautions should be given for women aged 40 or above with the realistic figures in that particular centre as they deserve to be informed of the lower cost-benefit.

Aggressive hyperstimulation regimes aiming at superovulation to increase the numbers of embryos to be replaced for the sake of achieving a higher pregnancy rate is not generally favoured because of the risks of hyperstimulation and complications of higher order pregnancies which could be detrimental to the women's health.

Therefore, utilization of oocyte donation and assisted hatching procedures as the measures to increase the fertility should be discussed with the older women before they commence receiving the ART treatments.

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