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Egg sharing for assisted conception: a window on oocyte quality

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Abstract   The steep decline in both natural fertility and success after assisted reproduction treatment with increasing maternal age is universally recognized. Large variations in the developmental competence of oocytes collected are seen during assisted cycles, and a link between the biological competence of oocytes retrieved and age has been confirmed. Patients who require donated oocytes can benefit from egg sharing programmes, in which a proportion of oocytes collected from selected patients aged ≤35 years undergoing conventional assisted reproduction treatment are shared with a matched recipient. The reproductive outcomes of the egg provider and recipient can thus be compared to quantify the significance of oocyte quality. Data gathered from two comparable treatment centres resulted in 285 pairs of egg sharing providers and their recipients that could be analysed statistically. The chief finding was donor pregnancy as a predictor of recipient pregnancy given embryo transfer (odds ratio 2.15, 95% confidence interval 1.33–3.46, $P \approx 0.002$), despite an appreciably higher mean age of the recipients. The probability of a recipient pregnancy increased by almost 0.2. Such results strongly indicate the key importance of oocyte quality for a successful clinical outcome in egg sharing practices and assisted reproduction treatment more generally.
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Introduction

Among the many factors affecting the prospects of a viable pregnancy, whether after natural or assisted conception (Elizur et al., 2005), the quality of the oocyte is one of the foremost. Following successful fertilization, the survival and development of the early embryo depend on organelles, mRNA and proteins that accumulated during oocyte growth and maturation, a complex process that continues throughout the reproductive lifespan (Albertini et al., 2003; Gosden and Lee, 2010). Fertility starts to decline significantly after the third decade, associated with a remarkable increase in

oocyte aneuploidy (Hassold and Hunt, 2001) and diminished ovarian reserve (Alviggi et al., 2009; Meldrum, 1993; te Velde and Pearson, 2002), which lower success rates with assisted reproduction treatments when women use their own eggs.

Ovarian stimulation is routinely used in clinical practice in order to obtain a large number of oocytes, although their developmental competence is highly variable and there is a high wastage rate. Only about 5–7% of fresh oocytes collected from young women result in a live birth, and this low figure decreases progressively to 1% at ≥40 years of age (Inge et al., 2005; Kovalevsky and Patrizio, 2005; Patrizio and Sakkas, 2009). Poor developmental competence is likely to be due at least in part to the developmental heterogeneity of follicles reaching 'mature' size after ovarian stimulation, but also to other factors since ageing profoundly affects natural fertility rates as well. The causes of oocyte ageing are poorly understood and no treatments are available for reversing its effects.

Consequently, donor oocytes are used for couples to help overcome infertility caused by diminished ovarian reserve and inability to conceive a viable pregnancy, as well as for other conditions including premature ovarian failure, surgical menopause and heritable genetic diseases. The trend for women to delay childbearing has also increased the number of assisted cycles worldwide that require donated oocytes due to diminished ovarian reserve or compromised oocyte quality related to age. The high success rates reported in oocyte recipients, irrespective of their age, are comparable to those of young women undergoing autologous assisted cycles, leading to the conclusion that age of the oocyte donor is the single most important factor predicting reproductive success (Abdalla et al., 1997; Cohen et al., 1999; Navot et al., 1991, 1994; Paulson et al., 1997; Toner et al., 2002; Zegers-Hochschild et al., 2010).

Oocyte donation cycles provide opportunities for studying factors that may be associated with the successful establishment of pregnancy, such as donor and recipient age and reproductive histories, endometrial thickness and pattern, ovarian reserve, number of embryos transferred, reproductive endocrinology, and obstetric-gynaecological and semen variables (Bodri et al., 2007; Garcia-Velasco et al., 2003; Harris et al., 2002; Levran et al., 1991; Noyes et al., 2001). However, specific recipient or cycle-related variables do not predict success or failure with high probability, apart from the general effect of age. The problem of investigation is compounded by variations in oocyte quality within a cohort from a given woman and between women of the same age after controlling for other factors. This fact has been noted when discordant outcomes were obtained in recipients sharing eggs from the same donor (Bodri et al., 2007; Garcia-Velasco et al., 2003) and was revealed statistically in a study of egg donation to two or three recipients (Harris et al., 2002). In the latter study, 85–90% of the variation in pregnancy and live birth outcomes could not be explained by specific donation characteristics, such as age and number of oocytes harvested. Donor heterogeneity due to oocyte quality (the 'donor effect') remains unexplained and under-investigated, yet is responsible for the failure of most oocyte donation treatment cycles.

Unfortunately, the underlying factors responsible for the donor effect cannot be revealed by clinical egg donation practice, and research into its biological foundations are constrained by the limited numbers of oocytes available. Genetic factors are likely to be important; a donor history of previous success accounted for 30% of the variation in live birth rates among recipients (Harris et al., 2002), but assessing this factor by twin studies or other standard methods is impractical.

Another source of information about the importance of oocyte variability, hitherto overlooked, is the clinical practice of egg sharing for assisted conception. The increasing demand for donated oocytes in assisted reproduction treatment cycles has resulted in acute shortages that cannot be met through the recruitment of altruistic donors. Oocyte-sharing schemes were developed to relieve chronic shortages in donor oocyte availability, which are especially acute in countries that prohibit financial compensation for the donors (Ahuja et al., 1996, 2000). The egg sharing provider (ESP) is a woman who requires IVF treatment in order to conceive and is willing to donate half of her oocytes (chosen at random) to a recipient (ESR) who needs them because of primary ovarian failure, risk of transmitting a genetic disease or has a poor response to stimulation/recurrent failure after treatment using her own oocytes. The IVF treatment of the egg recipient is incidental to the treatment of the egg provider, whose own treatment is subsidized by the recipient. Although reservations were initially expressed due to the possibility that the donor oocytes from infertile women might be of lower quality than those from altruistic donors, such concerns have not been substantiated in practice. In a recent study comparing cycle variables and outcome between egg sharing cycles and cycles that used oocytes from altruistic donors, Oyesanya et al. (2009) reached the conclusion that the outcomes were similar in terms of endocrine parameters, embryo quality, and implantation and pregnancy rates. The Human Fertilisation and Embryology Authority in the UK has approved the practice of egg sharing in licensed assisted reproduction treatment centres, with the proviso that adequate and independent counselling must be available to all couples who participate in egg sharing schemes (Human Fertilisation and Embryology Authority, 2000).

According to the hypothesis that oocyte quality is a chief determinant of fertility, subject to age-dependent and age-independent variation, the reproductive outcomes for the ESP and ESR after egg sharing, whether expressed as pregnancy or live birth rate, should be highly correlated. Confirmation will be relevant to assisted conception in general, since egg sharing does not compromise pregnancy or live birth rates for the donor (Oyesanya et al., 2009; Rimington et al., 2003; Thum et al., 2003).

Materials and methods

The study was based on data from two centres whose egg sharing programmes were established from comparable clinical and laboratory protocols: Bourn Hall Clinic, Cambridge (BHC, 2002–2008) and the London Women's Clinic, London (LWC, 2005–2008). The data were analysed for the years indicated in brackets and coded so that information that could potentially identify patients was completely eliminated. The oocytes from each ESP were donated anonymously to a

recipient of the same cytomegalovirus (CMV) status and ethnic group, and attempts were made to match the physical characteristics of ESP—ESR pairs as far as possible.

The ESPs, who were ≤36 years old (with only two aged 36 at the time of treatment) and with body mass index between 18—29 kg/m² were asked to complete a health questionnaire for medical, gynaecological and family history. They were screened by pelvic ultrasound scanning and blood tests were performed for basal reproductive endocrinology (FSH, LH and oestradiol on day 2/3 of a natural menstrual cycle), CMV, blood group type and blood factors (including anaemia), rubella, cystic fibrosis, chromosomal abnormalities, Venereal Disease Research Laboratory/*Treponema pallidum* haemagglutination tests, sickle cell anaemia, thalassaemia, HIV, hepatitis B and C, human T-lymphotrophic virus 1 and 2, chlamydia, gonorrhoea and Tay-Sachs disease (if indicated). The upper age limit for ESRs (54 years) was higher than for ESPs (36 years), but the mean ages of the same groups were similar between the two centres (Table 1). ESRs were assessed to exclude uterine pathology, and screened for blood group, CMV, HIV and hepatitis B and C, as well as undergoing additional counselling for the special implications of egg sharing.

The donors were prepared for ovarian stimulation by pituitary down-regulation with a GnRH agonist, either buserelin (Suprefact; Sanofi Aventis) 0.5 ml daily by subcutaneous injection or nafarelin (Synarel spray, Pfizer) 400 mg twice daily, starting in the luteal phase of the cycle before stimulation. After confirmation of down-regulation, ovarian stimulation was initiated with 150 IU of gonadotrophins (Gonal F or Puregon; MSD) and the cycles were monitored by ultrasound scan from day 6 of stimulation in order to confirm follicular growth. When necessary, the dosage of FSH was adjusted according to response. Ovulation was induced by human chorionic gonadotrophin (HCG) injection (Ovitrelle, Merck-Serono or Pregnyl, MSD) when the most advanced follicle had reached a diameter >18 mm with at least three additional follicles >14 mm; oocyte retrieval was carried out 36 h after HCG injection. After ultrasound-guided transvaginal oocyte retrieval, the donor's oocytes were divided randomly into equal numbers between herself and her ESR; in cases where an uneven number was

collected the additional oocyte was allocated to the ESP. The majority of oocytes were fertilized by intracytoplasmic sperm injection (ICSI) instead of standard insemination using either partner's spermatozoa or a sample of matched donor spermatozoa when required. BHC data included seven ESPs who required the use of donor spermatozoa, due to severe male infertility. No recipient cycles required donor spermatozoa. The total LWC cohort (*n* = 312) of ESP and ESR patients included 50 lesbian couples and 37 single women (28% of total). No heterosexual couples in the LWC cohort required use of donor spermatozoa.

The recipients were synchronized for embryo transfer either by down-regulation with a GnRH agonist (as described above for ESP) or administration of an oral contraceptive pill, Microgynon 30 (Bayer), one tablet daily, and the endometrium was prepared by hormone replacement therapy, oestradiol valerate 4 mg daily (Progynova; Schering). Progesterone administration with Cyclogest pessaries (Actavis) 400 mg daily or Crinone 8% (Merck-Serono) once daily was commenced the day after the donor received HCG, and adequate endometrial preparation was confirmed by an ultrasound scan before embryo transfer was scheduled. After culture in conditions that have been described previously (Elder, 2005), a maximum of two embryos were transferred to the uterus on day 2, 3 or 5 after insemination. The majority of the transfers were carried out on day 3 at LWC; at BHC, 30/258 transfers (11.6%) were carried out on day 5 after extended culture to the blastocyst stage and the remainder on day 3. No appreciable differences in outcome were detected for embryos transferred at the cleavage versus the blastocyst stage.

Data from paired patients who did not receive a fresh embryo transfer in the ESP stimulated cycle, either due to the risk of ovarian hyperstimulation syndrome (OHSS) or inadequate endometrial development in either donor or recipient, were excluded from further analysis because the pairs were not comparable. In these cases, embryo transfer was postponed by cryopreserving the embryos for a subsequent hormone replacement therapy-supplemented cycle. Eight ESP patients had all their embryos frozen due to the risk of OHSS, having generated >30 oocytes (average 33 oocytes). Following subsequent transfer of frozen

Table 1   Summary of embryology data and clinical outcomes after sharing eggs in two comparable assisted conception programmes.

Clinic	Patient group	No. of patients	Age (years)	Oocytes collected	No. of ICSI/IVF	Embryos created	Proportion of embryos/oocytes	No. of pregnancies	No. of live births
BHC	ESP	129	31.1 (22—35)	17.2 (8—39)	77/52	5.0 (1—13)	0.67 (0.071—1)	55	43
	ESR	129	41.2 (28—49)	—	85/44	4.4 (1—9)	0.65 (0.125—1)	64	41
LWC	ESP	156	30.5 (19—36)	16.1 (7—34)	136/20	5.6 (1—11)	0.68 (0.17—1)	79	67
	ESR	156	42.4 (28—54)	—	133/23	5.2 (1—11)	0.66 (0.14—1)	59	44

Values are mean (range) unless otherwise stated.
BHC = Bourn Hall Clinic; ESP = egg sharing provider (donor); ESR = egg sharing recipient; LWC: London Women's Clinic.

embryos from these cycles, one resulted in a live birth, one in a biochemical pregnancy and the remaining six had a negative result. Of the eight recipients who had fresh embryos transferred from these donors, three achieved healthy live births (one twin and two singleton deliveries). In another 11 cases, the endometrium of one of the pair had not developed sufficiently for implantation (<8 mm). After excluding these cases, a total of 285 egg sharing provider—recipient pairs were analysed, 129 pairs from BHC and 156 from LWC (Table 1).

The data were analysed using generalized linear modelling with a backwards elimination process (Francis et al., 1993). Statistical significance was assessed at the conventional P-value <0.05. All pregnancies, including biochemical (positive HCG on approximately day 15 post-fertilization) and miscarriages (after identification of viable fetal heart) were recorded, as were subsequent live births. Some of the statistical comparisons were made after dichotomising the data, notably for the number of oocytes ($\leq$20/>20) or age of the ESR ($\leq$35/>35 years).

Results

The patient characteristics and demographics, and the clinical and laboratory protocols were similar in the two centres. Indeed, the source of data was not a statistically significant covariate for either of the main outcomes, pregnancy given embryo transfer or live birth given pregnancy for both donors and recipients (after Bonferroni adjustment). As outlined in Table 1, the range of the age distributions for ESPs and ESRs was somewhat greater for the LWC (17 and 26, respectively) than BHC (13 and 21, respectively), although the mean ages (30.5 and 42.4, LWC; 31.1 and 41.2, BHC) did not differ much between centres. Likewise, the mean numbers of oocytes collected (16.1, LWC; 17.2, BHC) and embryos created (5.6 and 5.2, LWC; 5.0 and 4.4, BHC) were comparable between centres as well as between donors and recipients. Embryology data were expressed in numbers as well as proportions of the corresponding number of oocytes collected, to indicate fertilization rates. These proportions were very similar in all four groups (Table 1). ICSI was used in a majority of cycles,

but the distinction between ICSI/IVF was not considered a relevant factor for the outcomes since ICSI was not restricted to male factor indications in either clinic, and comparable studies found no influence of semen factors or male fertility (Bodri et al., 2007; Gallardo et al., 1996; Garcia-Velasco et al., 2003; Oehninger et al., 1998).

When potential covariates were tested for predictive effects on recipient pregnancy given embryo transfer, donor pregnancy was found to be highly significant with an odds ratio of 2.15 ($P \approx 0.002$) (Table 2). The estimated pregnancy probabilities were 0.53 for donor pregnant, and 0.34 for donor not pregnant. Hence, a donor pregnancy increased the probability of a recipient pregnancy by almost 0.2. None of the other covariates had additional significant effects, including the number or proportion of embryos created for the recipient, the number of oocytes harvested from the donor (either as a continuous variable or dichotomized) or the age of the recipient (either continuous or dichotomized).

The next best predictor of a recipient pregnancy without the donor pregnant covariate was donor live birth, the estimated odds ratio being 1.78 (95% CI 1.10—2.88) for live birth relative to no birth. When this covariate was omitted the donor proportion of embryos/oocytes was the next best predictor of a recipient pregnancy (odds ratio 1.08, 95% CI 0.96—1.21) for each 10 percentage-point increase in embryos/oocytes, with a slightly lower odds ratio (1.05, 95% CI 0.94—1.17) associated with the recipient proportion of embryos/oocytes.

None of the covariates significantly affected the chances of a recipient live birth given recipient pregnancy, the overall probability of this outcome being 0.69. Recipient age (continuous or dichotomized) was not a significant predictor of live birth. Interestingly, the best predictor of live birth (explaining most of the variation in this outcome) was the proportion of embryos/oocytes in the donor and not the recipient, with an estimated odds ratio of 1.15 (95% CI 0.97—1.38) for each 10 percentage-point increase in embryos/oocytes. However, this effect did not reach statistical significance (Table 2).

Unsurprisingly, increasing age of the donor was associated with the number of oocytes harvested ($P \approx 0.03$), with the mean number collected declining by an estimated factor of 0.94 for each additional 5 years of the donor's age

Table 2 Statistical analysis of the effects of covariates on clinical outcomes in two egg sharing programmes for assisted reproduction treatment.

Outcome measure	Probability of recipient pregnancy given embryo transfer	Probability of recipient live birth given pregnancy	Mean number of oocytes harvested (from donor)	Probability of donor pregnancy given embryo transfer	Probability of donor live birth given pregnancy
Covariate estimated effect	Donor pregnant odds ratio: 2.15	10 percentage-point increase in donor proportion embryos/oocytes odds ratio: 1.15	Additional 5 years on donor's age mean ratio: 0.94	10 percentage-point increase in donor proportion embryos/oocytes odds ratio: 1.17	Additional year on donor's age odds ratio: 0.91
95% CI	1.33—3.46	0.97—1.38	0.89—0.99	1.04—1.31	0.78—1.05
P-value	$\approx$0.002	NS	$\approx$0.03	$\approx$0.007	NS

NS = not significant.

(Table 2). The estimated mean numbers of oocytes at 20, 25, 30 and 35 years of age were 18.9, 17.8. 16.7 and 15.8, respectively.

Another anticipated finding was a significant covariate effect of the donor proportion of embryos/oocytes on donor pregnancy ($P \approx 0.007$). This was a modest effect, however, the estimated odds ratio being only 1.17 (95% CI 1.04–1.31) for each 10 percentage-point increase in the proportion. The estimated probabilities of a donor pregnancy were 0.31, 0.40, 0.50 and 0.60 for 25%, 50%, 75% and 100% donor embryos/oocytes, respectively. The overall probability of a donor live birth given pregnancy was 0.82 and none of the covariates had significant effects on this measure of outcome (Table 2). This donor live birth rate was significantly ($P \approx 0.02$) higher than the recipient live birth rate (0.69), reflecting the generally younger ages of the donors compared with the recipients (Table 1).

Discussion

One of the most remarkable facts of human reproduction is its extraordinary inefficiency. In natural fertility populations, this is measured as the time to conception for women trying to get pregnant, but assisted reproduction affords opportunities for close monitoring, albeit of infertile couples. From a biological standpoint, it makes sense to index female fertility as the number of live births for every 100 oocytes collected during an assisted reproduction cycle, because oocytes are a limiting factor. Generally in successful treatment centres, the index has been found to be approximately 4–5% for women aged less than 35 years using their own oocytes, or slightly higher when they use young donor oocytes, but it declines to or below 1% in older women (Inge et al., 2005; Martin et al., 2010; Patrizio and Sakkas, 2009). Interestingly, these percentages have hardly changed since the pioneering work of Edwards and Steptoe in the early 1980s, implying that oocyte quality has not significantly improved during the evolution of ovarian stimulation protocols (Inge et al., 2005). Biological factors are presumably chiefly responsible for the high rates of oocyte wastage.

Yet it is clear from clinical practice that, although the majority of oocytes in cohorts collected after controlled ovarian stimulation are not developmentally competent for conception, there is much variation between individual women, associated with age as well as with age-independent factors. Assisted reproduction can again shed light on the variation. In a study of women who donated eggs on more than one occasion, wide differences in pregnancy success among their recipients were reported, despite the donors being uniformly young and presumptively, if not already proven, fertile. At one end of the spectrum, some donors could be regarded as 'superfertile', achieving high success rates, whereas at the other end some never succeeded in helping any recipient to achieve pregnancy and live birth (Harris et al., 2002). This phenomenon, termed the 'donor effect', is familiar in clinical practice and has been reported from other centres (Bodri et al., 2007; Garcia-Velasco et al., 2003). If oocyte quality could be improved through a better understanding of the biological character of this donor effect, the benefits for reproductive care would be greater than from any other breakthrough currently envisioned.

The new data presented here reinforce these conclusions based on egg sharing in two collaborating centres. The chief difference with conventional egg donation is that ESPs can be regarded as a kind of control, because their oocytes are equally and randomly shared with ESRs. According to the hypothesis that oocyte quality overwhelmingly determines the success of assisted reproduction treatment in young as well as ageing women, there should be a close correlation of the pregnancy rates within ESP–ESR pairs; this was confirmed by a highly significant odds ratio and an increase of almost 0.2 in the probability that the ESR will be successful if the ESP became pregnant using oocytes from the same cohort. These findings are all the more striking in view of differences in age between the two groups. When strong candidates are identified (molecules or organelles) to account for variations in oocyte competence, the eggs of women with a history of either high or low pregnancy success after egg donation/sharing will provide unrivalled opportunities for experimental validation and, potentially, for improving clinical outcomes with assisted reproduction treatments more generally.

In contrast, other covariates analysed were either barely significant or non-significant, or already familiar facts of assisted reproduction treatment. There was an inverse relationship between donor age and the number of oocytes harvested, but although this is consistent with the decline in total ovarian reserve, at 6% decrease in number every five years, it does not proceed at the same rate as attrition (Faddy et al., 1992). Differences between the rate of loss of follicles *in toto* (mainly primordial follicles) and follicles that reach ovulation size after stimulation imply that the ageing ovary allows a larger proportion of follicles to grow to maturity either by accelerating the rate of recruitment or by reducing atresia. Whether changes in follicle dynamics have any bearing on the observed decline in oocyte quality is however conjectural. The only other significant covariate was the ratio of embryos/oocytes, which predicted the chance of pregnancy after embryos were transferred to the donor. Since this ratio reflects the fertilization rate, itself a key criterion of oocyte quality, this conclusion was expected.

Acknowledgements

References

Abdalla, H., Wren, M., Thomas, A., Korea, L., 1997. Age of the uterus does not affect pregnancy or implantation rates; a study of egg donation in women of different ages sharing oocytes from the same donor. Hum. Reprod. 12, 827–829.

Ahuja, K.K., Simons, E.G., Fiamanya, W., et al., 1996. Egg-sharing in assisted conception: ethical and practical considerations. Hum. Reprod. 11, 1126–1131.

Ahuja, K.K., Simons, E.G., Rimington, M.R., et al., 2000. One hundred and three concurrent IVF successes for donors and recipients who shared eggs: ethical and practical benefits of egg sharing to society. Reprod. BioMed. Online 1, 101–105.

Albertini, D.F., Sanfins, A., Combelles, C.M., 2003. Origins and manifestations of oocyte maturation competencies. Reprod. BioMed. Online 6, 410–415.

Alviggi, C., Humaidan, P., Howles, C.M., Tredway, D., Hillier, S.G., 2009. Biological versus chronological ovarian age: implications for assisted reproductive technology. Reprod. Biol. Endocrinol. 22, 7–101.

Bodri, D., Colodron, M., Vidal, R., Galindo, A., Durban, M., Coll, O., 2007. Prognostic factors in oocyte donation: an analysis through egg-sharing recipient pairs showing a discordant outcome. Fertil. Steril. 88, 1548–1553.

Cohen, M., Lindheim, S.R., Sauer, M.V., 1999. Donor age is paramount to success in oocyte donation. Hum. Reprod. 14, 2755–2758.

Elder, K.T., 2005. Routine gamete handling: oocyte collection and embryo culture. In: Brinsden, P. (Ed.), A Textbook of In Vitro Fertilization. Taylor-Francis, London, pp. 287–308.

Elizur, S.E., Lerner-Geva, L., Levron, J., Shulman, A., Bider, D., Dor, J., 2005. Factors predicting in-vitro fertilization treatment outcome: a multivariate analysis of 5310 cycles. Reprod. Biomed. Online 10, 645–649.

Faddy, M.J., Gosden, R.G., Gougeon, A., Richardson, S.J., Nelson, J.F., 1992. Accelerated disappearance of ovarian follicles in mid-life – implications for forecasting menopause. Hum. Reprod. 7, 1342–1346.

Francis, B., Green, M., Payne, C., 1993. The GLIM System: Release 4 Manual. Clarendon Press, Oxford.

Gallardo, E., Simon, C., Levy, M., Guanes, P.P., Remohí, J., Pellicer, A., 1996. Effect of age on sperm fertility potential: oocyte donation as a model. Fertil. Steril. 66, 260–264.

Garcia-Velasco, J.A., Isaza, V., Caligara, C., Pellicer, A., Remohí, J., Simón, C., 2003. Factors that determine discordant outcome from shared oocytes. Fertil. Steril. 80, 54–60.

Gosden, R.G., Lee, B., 2010. Portrait of an oocyte: our obscure origin. J. Clin. Invest. 120, 973–983.

Harris, S.E., Faddy, M., Levett, S., Sharma, V., Gosden, R., 2002. Analysis of donor heterogeneity as a factor affecting the clinical outcome of oocyte donation. Hum. Fertil. 5, 93–198.

Hassold, T., Hunt, P., 2001. To err (meiotically) is human: the genesis of human aneuploidy. Nat. Rev. Genet. 2 (4), 280–291.

Human Fertilisation and Embryology Authority, 2000. Guidance for Egg Sharing Arrangements. Human Fertilisation and Embryology Authority, London.

Inge, G.B., Brinsden, P.R., Elder, K.T., 2005. Oocyte number per live birth in IVF: were Steptoe and Edwards less wasteful? Hum. Reprod. 20, 588–592.

Kovalevsky, G., Patrizio, P., 2005. High rates of embryo wastage with use of assisted reproductive technology: a look at the trends between 1995 and 2001 in the United States. Fertil. Steril. 84, 325–330.

Levran, D., Ben-Shlomo, I., Dor, J., Ben-Rafael, Z., Nebel, L., Mashiach, S., 1991. Aging of endometrium and oocytes: observations on conception and abortion rates in an egg donation model. Fertil. Steril. 56, 1091–1094.

Martin, J.R., Bromer, J.G., Sakkas, D., Patrizio, P., 2010. Live babies born per oocyte retrieved in a subpopulation of oocyte donors with repetitive reproductive success. Fertil. Steril. (advance pub online).

Meldrum, D., 1993. Female reproductive aging − ovarian and uterine factors. Fertil. Steril. 59, 1–5.

Navot, D., Bergh, P.A., Williams, M.A., et al., 1991. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. Lancet 337, 1375–1377.

Navot, D., Drews, M.R., Bergh, P.A., et al., 1994. Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. Fertil. Steril. 61, 97–101.

Noyes, N., Hampton, B.S., Berkeley, A., Licciardi, F., Grifo, J., Krey, L., 2001. Factors useful in predicting the success of oocyte donation: a 3-year retrospective analysis. Fertil. Steril. 76, 92–97.

Oehninger, S., Chaturvedi, S., Toner, J., et al., 1998. Semen quality: is there a paternal effect on pregnancy outcome in in-vitro fertilization/intracytoplasmic sperm injection? Hum. Reprod. 13, 2161–2164.

Oyesanya, O.A., Olufowobi, O., Ross, W., Sharif, K., Afnan, M., 2009. Prognosis of oocyte donation cycles: a prospective comparison of the in vitro fertilization–embryo transfer cycles of recipients who used shared oocytes versus those who used altruistic donors. Fertil. Steril. 92, 930–936.

Patrizio, P., Sakkas, D., 2009. From oocyte to baby: a clinical evaluation of the biological efficiency of in vitro fertilization. Fertil. Steril. 91, 1061–1066.

Paulson, R., Hatch, I., Lobo, R., Sauer, M., 1997. Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. Hum. Reprod. 12, 835–839.

Rimington, M.R., Ahuja, K.K., Simons, E.G., et al., 2003. Should non-patient volunteers donate eggs? Reprod. Biomed. Online 6, 277–280.

te Velde, E.R., Pearson, P.L., 2002. The variability of female reproductive ageing. Hum. Reprod. Update 8, 141–154.

Thum, M.Y., Gafar, A., Wren, M., et al., 2003. Does egg-sharing compromise the chance of donors or recipients achieving a live birth? Hum. Reprod. 18, 2363–2367.

Toner, J.P., Grainger, D.A., Frazier, L.M., 2002. Clinical outcomes among recipients of donated eggs: an analysis of the U.S. national experience, 1996–1998. Fertil. Steril. 78, 1038–1045.

Zegers-Hochschild, F., Masoli, D., Schwarze, J.-E., Iaconelli, A., Borges, E., Pacheco, I.M., 2010. Reproductive performance in oocyte donors and their recipients: comparative analysis from implantation to birth and lactation. Fertil. Steril. 93, 2210–2215.