Human Reproduction Update 1999, Vol. 5, No.5 p. 546–550 © *European Society of Human Reproduction and Embryology*

The fertility potential of women with a single ovary

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The incidence of having a single ovary is quite common in infertile patients and can reach up to 17% of women with severe tubal disease who require in-vitro fertilization (IVF) treatment. Data on the short- and long-term implications of having only one ovary are scarce, and patients in this situation are naturally concerned. This article reviews the effect of possessing a single ovary on the fertility potential and ovarian reserve of these women and their performance in assisted reproduction treatment.

Key words: in-vitro fertilization/oophorectomy/ovarian reserve/single ovary

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Introduction

Through turbulent events of life, some women have only one ovary when they are in their reproductive period. The absence of both ovaries manifests itself clearly by infantile sexual development, primary amenorrhea and primary infertility (Gold *et al.*, 1997), or by a menopause status following surgical removal of the ovaries if it occurs at a later stage in life. The absence of a single ovary has, in contrast, no clinical symptoms. Most of these women can recall a previous surgery in which one ovary had been removed, while for others it is an incidental finding during an infertility investigation or exploratory laparotomy. The real prevalence of women with a single ovary in the normal population, or even in the subfertile group, is not known. In one study (Goswamy *et al.*, 1988), 2221 healthy postmenopausal women were screened by pelvic ultrasonography; the left ovary was detected in 99.1% of these women, and the right ovary in 98.9%. The incidence in tubal factor infertility patients is not documented, but is probably higher. These patients have a history of pelvic disease and some of them have undergone pelvic surgery. In one report (Lam *et al.*, 1987), 34 women with a single ovary were identified among 369 women (9.2%) with severe tubal disease who had laparoscopic oocyte retrieval, while in a subsequent study (Boutteville *et al.*, 1987), a series of tubal infertility patients having in-vitro fertilization (IVF) treatment was reported in which 17% (86/501) of women had a single ovary. We have shown that, of 1061 women diagnosed with pure tubal disease and started on IVF treatment, 58 (5.5%) had had unilateral oophorectomy (Lass *et al.*, 1997a). The finding of a single ovary is therefore more common than might be expected, and can occur in up to 17% of women with severe tubal disease who require IVF treatment.

Surprisingly, the fertility potential of women with a single ovary has not been explored, and few data are available in the literature. The real prospects of women with one ovary are a cause for concern to patients and medical teams alike. The purpose of this review is to summarize the currently available data in the literature on women having a single ovary, and in particular the clinical implications of the absence of an ovary on the fertility potential of these women.

Aetiology of single ovary

Congenital absence of the ovary with or without absence of the Fallopian tube is rare event (Eustace, 1992). There are two possible explanations for this phenomenon. The first is a defect in the development of the entire Müllerian and mesonephric systems on one side, or a defect localized to the region of the genital ridge and the caudal part of the Müllerian duct (Dare

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et al., 1989). The second explanation is that, occasionally, an ovary which is parasitic to the omentum or to other intra-abdominal structures, and is completely separate from its normal attachment, is encountered. This condition is caused by torsion of the ovarian pedicle, which can occur asymptomatically in adult life or childhood, or even before birth (James *et al.*, 1970; Aslam *et al.*, 1995). A free-floating, calcified cyst was found in the peritoneal cavity in association with unilateral absence of the adnexa (Silva *et al.*, 1995); these authors speculated that this had occurred due to torsion and separation of the adnexa from their supporting structures. In another study (Dabirashrafi *et al.*, 1994), a higher incidence of malposition of the ovary was found in patients with either an absent or unicornis uterus. These women may be therefore at increased risk for ovarian torsion and, consequently, for an absent ovary.

The incidence of single ovary as a result of the first explanation is much lower than as a result of the second. Indeed, it is estimated that the incidence of true congenital unexplained unilateral absence of the ovary and Fallopian tube is only one in 11 240 women (Sivanesaratnam, 1986).

A more common aetiology arises in women who have had unilateral oophorectomy for various reasons (this group of patients comprised the vast majority of women with a single ovary). The most common reasons include ovarian mass or cyst (benign or malignant), tubo-ovarian abscess, torsion of the ovary, endometrioma or ruptured ectopic pregnancy. In the largest reported series of patients who had undergone unilateral oophorectomy before IVF treatment ($n = 153$), the aetiological distribution was as follows: ovarian endometriosis, 47%; pelvic inflammatory disease, 22.2%; benign ovarian cyst, 15.7%; and ectopic pregnancy, 15% (Khalifa *et al.*, 1992).

Fertility in natural conceptions

Currently, there are no data available on the fecundity of women with a single ovary. Animal studies carried out in rabbits, cats, mice and pigs on natural cycles have shown an ovarian hypertrophy and compensatory ovulatory rate after unilateral oophorectomy (Lipschutz, 1924–1925; Dailey *et al.*, 1969). Previously, it had been shown in mice (Biggers *et al.*, (1962) that when one ovary was removed, the other underwent hypertrophy so that its weight became similar to that of two intact ovaries. In a later study (Pakrasi *et al.*, 1992), it was shown that mice which had been mated one day after unilateral ovariectomy had a reduced implantation rate and ovarian weight. However, ovarian weight and implantation rates increased when mating was performed more than one day after surgery, and peaked at 19–21 days. These findings confirmed the rapid compensation of the single ovary, even if the mice became pregnant. It was suggested (Butcher, 1977; Gibson *et al.*, 1979) that the ovarian hypertrophy was most likely caused by increased secretion of pituitary gonadotrophin, although the compensation was incomplete, the mice had fewer litters, and they stopped breeding at a younger age than did mice with two ovaries. An elegant study was conducted to investigate the compensatory mechanism of a single ovary of the lizard *Anolis carolinensis* (which has asymmetric ovarian growth) (Roth and Jones, 1992). In one group of lizards, the large ovary was removed, while in a control group a sham operation was performed. Both groups were stimulated with ovine follicle stimulating hormone (FSH) following surgery. The response of the small ovary was significantly greater in the ovariectomized lizards than in the controls, the results demonstrating a greater sensitivity of the small ovary to FSH if the large ovary was absent.

Such a compensatory effect is not known in humans, and while transvaginal measurements of ovarian volume have few useful clinical implications in assessing ovarian activity (Lass and Brinsden, 1999), no studies have been conducted to confirm lack of ovarian hypertrophy in women.

Fertility in assisted conception

Some women who have a single ovary may subsequently be infertile. Presumably, the cause of their infertility is tubal damage following surgical treatment and consequently they are often treated by IVF. Conflicting reports exist concerning the effect of unilateral oophorectomy on IVF outcome with different stimulation protocols (Table I).

In an early study (Diamond *et al.*, 1984), it was shown that women with two ovaries have higher serum oestradiol concentrations than women with a single ovary, following stimulation with either clomiphene citrate (CC) or human menopausal gonadotrophin (HMG); however, the number of oocytes retrieved was similar in both groups. In subsequent studies (Alper *et al.*, 1985; Dodds *et al.*, 1987) it was found that, although patients with one ovary required a longer period of induction, their total amount of HMG, peak serum oestradiol concentrations, number of large follicles, number of oocytes retrieved and clinical pregnancy rate were the same as for women with two ovaries. It was later concluded (Alper *et al.*, 1987) that although follicular fluid (FF) oestradiol concentrations were lower in patients with one ovary, this dysynchrony between oocyte maturity and FF oestradiol concentration did not appear to affect IVF outcome adversely. In 1993, using a gonadotrophin-releasing hormone agonist (GnRHa)/HMG protocol, it was shown that women with one ovary are at no reproductive disadvantage when compared to women with two ovaries when undergoing ovulation induction for IVF (Penzias *et al.*, 1993). However, the patient group in this study ($n = 7$) was too small to draw meaningful conclusions.

Table I. Summary of studies on in-vitro fertilization (IVF) treatment in women with a single ovary

Reference	No. of patients with single ovary	Mean patient age (years)	Stimulation protocol	Outcome measured for women with single ovary compared with both ovaries *in situ*
Diamond *et al.* (1984)	38	NA	CC = 16 HMG = 22	Less follicles, similar number of oocytes
Alper *et al.* (1985)	14	32.8	CC + HMG	Less follicles and oocytes, similar PR
Alper *et al.* (1987)		34.3	CC + HMG	Similar stimulation dose and peak oestradiol concentrations, less oestradiol in follicular fluid. No clinical outcome
Boutteville *et al.* (1987)	86	32.3	HMG	Fewer oocytes, identical PR
Dodds *et al.* (1987)	16	32.3	CC + HMG or CC alone	Similar peak oestradiol concentrations, and number of follicles, oocytes, embryos and PR
Dodson *et al.* (1987)	23	NA	HMG	Less oestradiol concentrations per follicle and number of follicles and oocytes. The same HMG dose, similar fertilization rate, PR
Lam *et al.* (1987)	34	31	CC + HMG	Less follicles and oocytes, higher fertilization rate, similar PR
Khalifa *et al.* (1992)	162 cycles; no. of women, NA	34.6	HMG/FSH	Higher basal FSH concentrations, less
Penzias *et al.* (1993)	7	NA	GnRHa +	Similar oestradiol concentrations and
Nargund and	17	30.6 (all	GnRHa +	Similar dose of stimulation and peak
Bromham (1995)		<38 years)	FSH	oestradiol concentrations. Less follicles and oocytes, lower clinical PR
Lass *et al.* (1997a)	58	34.5	GnRHa + HMG	More FSH stimulation, lower oestradiol, fewer follicles and oocytes. Similar fertilization and pregnancy rates
Lass *et al.* (1997c)	73	34.2	GnRHa + HMG	Compared left to right ovary; similar response and PR

CC = clomiphene citrate; GnRHa = gonadotrophin releasing hormone agonist; HMG = human menopausal gonadotrophin; NA = not available; PR = pregnancy rate.

In contrast, we and others (Boutteville *et.*, 1987; Dodson *et al.*, 1987; Lam *et al.*, 1987; Khalifa *et al.*, 1992; Nargund and Bormhan, 1995; Lass *et al.*, 1997a) showed that women who had undergone unilateral oophorectomy responded less well to ovarian stimulation than women with both ovaries in terms of number of follicles, concentrations of oestradiol and number of oocytes retrieved. Moreover, these women required a higher dose of gonadotrophins (Lass *et al.*, 1997a). Pregnancy rates in women with a single ovary were similar to those in women with both ovaries in all these studies except two (Khalifa *et al*., 1992; Nargund and Bormhan, 1995) in which a lower clinical pregnancy rate was found in the single-ovary group; however, the latter finding did not reflect in a significantly reduced on-going pregnancy rate (13%) compared with women who had both ovaries (18%). It appears therefore, that once women with a single ovary achieve the stage of embryo transfer, they can be reassured that their chance of having a child are the same as women with two intact ovaries.

Single ovary and ovarian reserve

The sum of the evidence from the studies outlined above suggest that women with a single ovary have reduced ovarian reserve, basically because of depletion of the total number of primordial follicles in their ovary, and not because of a reduced quality of the oocytes. From over 250 000 early follicles at menarche, only a few hundred or thousand remain at the end of reproductive life (Block, 1952; Baker, 1963). This loss—which is age-related (Lass *et al.*, 1997b)—accelerates at about the age of 37 years old and precedes the menopause by 10–12 years (Richardson *et al.*, 1987; Faddy and Gosden, 1995, 1996). There are individual variations in the number and rate of depletion of follicles, but women with a single ovary probably reach this critical threshold earlier. Currently, the serum FSH concentration is the best marker to assess ovarian reserve and of predicting response to superovulation, with a good correlation to pregnancy rates (Scott *et al.*, 1989; Toner *et al.*, 1991). In a later study (Khalifa *et al.*, 1992), the impact of unilateral oophorectomy on basal FSH concentrations was evaluated, and it was shown that the 162 women with one ovary had higher basal FSH concentrations and poorer response to stimulation than the 1066 women with two ovaries; more importantly, this was not an age-related effect. The higher concentration of FSH in women with a single ovary is probably a marker for the depleted ovarian reserve and, after controlling the FSH concentrations, the differences in responsiveness to ovarian

stimulation of pregnancy and delivery rates between the two groups vanished. The data obtained from the study indicated that basal FSH screening retains its predictive value in women with one ovary, even when the same threshold for defining an abnormal test is used (Sharara *et al.*, 1998). Later, it was concluded in a review on risk factors of the menopause (Cramer and Xu, 1996), that the effect of losing one ovary is less well documented than other relevant factors. In an earlier study (Cramer *et al*., 1995), it had been found that women who had lost one ovary at an early age—particularly before the age of 35 years—had a strong risk factor for early menopause. Women who have multiple risk factors, including smokers who have accumulated more than 10 pack-years, those estimated to have had more than 300 ovulatory cycles, those women with a history of depression, and those who have a family history of early menopause, have the greatest shift in the probability of early menopause.

It appears that unilateral oophorectomy can significantly adversely affect the fertility potential of women who already have suspected reduced ovarian reserve (i.e. those in their late thirties to early forties, with raised basal FSH concentrations, and reduced basal inhibin-b concentrations).

Predilection of one ovary?

In the non-human primate, it is suggested that ovulation occurs in equal frequency in the right and left ovary (Wallach *et al.*, 1973). In the human, some controversy remains about the frequency of ovulation in each side. In one study (DiZerega and Hodgen, 1982), it was shown that there is no clear preference of one ovary over the other during consecutive cycles. Later, it was demonstrated that in spontaneously ovulating women, right-sided ovulation occurred in 64% of cases compared with 36% left-sided ovulation (Potashnik *et al*., 1987). Subsequently, it was shown in 123 women undergoing 410 natural cycles of infertility treatment (103 intrauterine insemination and 143 IVF) that ovulation rates were similar in both ovaries [210 of 410 (51%) were on the right side] (Fukuda *et al*., 1996). The results of an additional study (Balasch *et al*., 1994) also contradicted those of the earlier study (Potashnik *et al.*, 1987) by showing that, in 156 unstimulated IVF cycles, 52% of ovulations were on the right side, and 48% on the left (this was not statistically significant). It was found that the side of ovulation correlated to the length of the follicular phase, with contralateral ovulation as compared with the preceding cycle occurring in 72% of cycles with a follicular phase <13 days (Fukuda *et al*., 1996). In cycles with a short follicular phase, the residual corpus luteum from the previous cycle may prevent the development of a dominant follicle in that ovary by local activity, and ovulation therefore tends to occur in the contralateral ovary. In cycles with a follicular phase >14 days, the diminished local corpus luteum activity enables dominant follicular development from either ovary at random. This study was later extended (Fukuda *et al*., 1998) to investigate the effect of clomiphene citrate stimulation on the side of ovulation in 363 cycles. The results confirmed the findings of the natural cycles with, in contralateral ovulations, the follicular phase being significantly shorter than that of the ipsilateral ovulations. An additional study (Driscoll *et al*., 1996) showed that, for ovulation induction for gamete intra-Fallopian transfer (GIFT) in women with both ovaries, there was a slight skew towards right ovary predominance but this was not statistically significant. Moreover, no relationship was found between pregnancy rate and the placement of gametes into the Fallopian tube which was coincident with the dominant ovary.

We have compared 56 cycles in 44 women after left oophorectomy, with 42 cycles in 29 women following right oophorectomy (Lass *et al.*, 1997c). There was no difference in total amount or days of HMG required for superovulation, peak oestradiol concentrations, number of oocytes retrieved, and fertilization rate. Moreover, the pregnancy rate was identical in the two patient groups. In an investigation in women after unilateral oophorectomy, similar numbers of follicles and oocytes were found in the right and left ovaries (Nargund and Bromham, 1995). These authors' results, in line with ours, indicate that with GnRHa/HMG/FSH ovulation induction protocols for IVF, there is no predilection of one ovary over the other. Among 200 consecutive patients with healthy ovaries who were having IVF treatment, the ovarian response, embryo production and pregnancy rates were similar for the right and left ovaries (Thomson *et al.*, 1998). Therefore, in women it is safe to conclude that although differences exist in the anatomical relationship and venous drainage of the two ovaries, there is no predilection of one ovary over the other.

Conclusions

In summary, women with a single ovary—be it right or left—do not in general have a reduced fertility potential to conceive, either naturally or via IVF treatment. However, women have no compensatory mechanism for the loss of one ovary and, as the number of primordial follicles in the ovary is finite, these women may have a shorter reproductive life span. The possession of only one ovary may be crucial in women who already have diminished ovarian reserve, and further clinical studies need to be conducted in order to assess the full impact of this situation.

Acknowledgements

The author wishes to thank Mr Peter Brinsden, FRCOG, Medical Director, and Mike Macnamee PhD, of Bourn Hall Clinic, for their useful comments and critical review of this manuscript.

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Received on April 7, 1999; accepted on June 24, 1999