

Biological Impact of Unilateral Oophorectomy: Does the Number of Ovaries Really Matter?

Biologische Auswirkungen der einseitigen Ovariectomie: Kommt es wirklich auf die Anzahl der Eierstöcke an?



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ABSTRACT

Although unilateral oophorectomies are performed more often than bilateral ones in women of reproductive age, their clinical consequences have been less intensively investigated. Experimental models in animals have shown that compensatory mechanisms occur after a unilateral oophorectomy (UO). This review aims to summarize the available evidence on the biological effects of unilateral oophorectomy on women. Evaluated outcomes include age at onset of menopause, risk of cardiovascular and neurological disease, risk of mortality and fertility outcome after spontaneous conception or in vitro fertilization (IVF). Results were compared with findings reported after bilateral oophorectomy and/or ovarian excision and/or women with intact ovaries. An electronic database search was performed using PubMed and Scopus, followed by a manual search to identify controlled studies that compared women after UO with women with two intact ovaries. In particular, a systematic review of fertility outcomes after IVF was performed, and the data were summarized in a table. Women who underwent UO had a similar age at menopause and similar clinical pregnancy rate compared to women with two ovaries. However, decreased ovarian reserve affecting the quantity but not the quality of the ovarian pool after IVF was observed in the UO group. Furthermore, an increased risk of neurological disease and even an increased risk of mortality was observed in women with single ovary. These data need to be confirmed by further studies, and a plausible mechanism of action must be identified. At present, patients who undergo UO can be reassured with regard to their reproductive potential and their age at onset of menopause.

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ZUSAMMENFASSUNG

Obwohl einseitige Ovariectomien häufiger als bilaterale Eierstockentfernungen bei Frauen im reproduktionsfähigen Alter durchgeführt werden, hat man den klinischen Folgen von einseitigen Ovariectomien weniger Aufmerksamkeit gewidmet. Experimentelle Tiermodelle zeigen, dass Kompensationsmechanismen nach einseitigen Ovariectomien stattfinden. Ziel dieser Übersichtsarbeit war es, die existierenden Forschungsergebnisse zu den biologischen Auswirkungen von einseitigen Ovariectomien zusammenzufassen. Zu den untersuchten Aspekten zählten Alter bei Eintritt der Wechseljahre, Risiko für Herz-Kreislauf-Erkrankungen und neurologische Erkrankungen, Mortalitätsrisiko und Fertilitätsergebnis nach spontaner Empfängnis oder In-vitro-Fertilisation (IVF). Diese Ergebnisse wurden mit den Ergebnissen nach bilateraler Ovariectomie und/oder ovarieller Exzision bzw. von Frauen mit intakten Eierstöcken verglichen. Es wurde zunächst eine elektronische Datenbanksuche mithilfe von PubMed und Scopus durchgeführt. Danach wurde eine manuelle Suche durchgeführt, um kontrollierte Studien auszumachen, die Frauen

nach einseitiger Ovariectomie mit Frauen mit 2 intakten Eierstöcken verglichen. Es wurde eine systematische Überprüfung der Fertilitätsergebnisse nach IVF durchgeführt, und die Daten wurden in einer Tabelle zusammengefasst. Bei Frauen, die sich einer einseitigen Ovariectomie unterzogen hatten, waren das Alter bei Eintritt der Wechseljahre sowie die klinischen Schwangerschaftsraten ähnlich wie bei Frauen mit 2 Eierstöcken. Es wurde zwar eine verminderte ovarielle Reserve bei Frauen nach einer einseitigen Ovariectomie festgestellt; diese wirkte sich aber auf die Quantität, nicht auf die Qualität des ovariellen Pools nach IVF aus. Es wurde ferner ein erhöhtes Risiko für neurologische Erkrankungen und sogar ein erhöhtes Mortalitätsrisiko bei Frauen mit nur einem Eierstock beobachtet. Diese Daten müssen in weiteren Studien bestätigt werden, und ein plausibler Wirkungsmechanismus dafür muss noch identifiziert werden. Nach aktuellem Wissensstand können Patientinnen, die sich einer einseitigen Ovariectomie unterziehen, hinsichtlich ihres reproduktiven Potenzials und ihres Alters bei Eintritt der Wechseljahre beruhigt sein.

Introduction

Adnexal surgery is one of the most common surgeries performed by gynecologists in clinical practice. When it is performed in women of reproductive age, surgical technique will aim to preserve as much parenchymal tissue as possible so as to preserve endocrine and reproductive function. Unfortunately, a parenchyma-preserving approach is not always possible and the entire ovary may have to be removed. This is the case when the physician finds a suspicious mass, an ovarian malignancy or a lesion that has replaced the entire parenchyma. Interestingly, Laughlin-Tommaso et al. observed that in 1838 women subjected to unilateral oophorectomy (UO) before menopause, the most frequent cause of unilateral ovarian resection was a benign condition (73.6%), with non-malignant ovarian cysts the most common pathological finding (58.6%) [1].

Fertility and endocrine consequences after bilateral oophorectomy are clear, with abrupt cessation of fertility and immediate menopause. Several other consequences affecting women's overall health, such as increased risk of cardiovascular and neurological disease and an increased overall risk of mortality, have been reported [2–6].

On the other hand, relatively little is known about the consequences of unilateral oophorectomy (UO). The remaining ovary after UO maintains sufficient endocrine function to avoid the occurrence of symptoms linked to bilateral oophorectomy. However, there is still relatively little knowledge about the long-term effects on women's overall health and the reproductive potential of women who have had UO.

This review aims to summarize the current evidence about the biological impact of UO. Published studies on women who had unilateral oophorectomy which reported on the impact of UO on age at onset of menopause and/or risk of cardiovascular and/or neurological disease and/or mortality risk as well as fertility were

included and summarized. An overview of the known biological effects of UO in animal models is also given.

Review

Unilateral oophorectomy in experimental animal models

The biological effects relating to UO have been extensively studied in different animal species. The detailed biological evidence from the animal kingdom can help to obtain a better understanding of the physiological phenomenon that occurs in the remaining ovary after the removal of the contralateral gonad.

In fishes, UO is associated with an increase in mass of the contralateral ovary and the reduction of follicular atresia. The growth of the remaining ovary seems to be related to an increase in the number and size of mid-to-late stage follicles without any recruitment of new primary oocytes [7]. Plasma steroid levels of fishes subjected to oophorectomy were found to be similar to those of a control group with two intact ovaries [8]. In this case, GnRH/FSH hormones appeared to be the basic regulators of the compensatory process [8].

Similar mechanisms seem to be involved in the compensatory phenomenon occurring in ovariectomized mammals. Studies carried out in rats and cows showed that the short and long-term effects of UO do not include a reduction of follicular reserve in the contralateral ovary. Even in mammals, no additional recruitment of primordial follicles occurs but the ovulatory rate within the growing follicles increases, thus allowing multiple ovulations during the same ovarian cycle. In contrast to what was observed in fishes, the number of follicles undergoing atresia in the remaining ovary remains stable, thus suggesting that the fertility preservation is not related to a reduction in atresia [9–10]. In sheep subjected to UO, compensatory mechanisms involving the remaining ovary were observed only at the end of the estrous cycle in which

surgery was performed [11]. Immediately after surgery, the higher ovulation rate was found to be related to ovulations from multiple follicular waves of the cycle, caused by prolongation of the static phase of the largest follicle of the penultimate wave. These dynamics appeared not to be LH or FSH dependent.

Moreover, evidence about rats suggests that the two ovaries play distinct homeostatic roles and that ovarian surgery may affect the fertility potential differently, based on which ovary is removed. Two different studies revealed that the right and left ovary play different roles in maintaining normal hormone levels, that these roles change cyclically during the course of the ovarian cycle, and that the effect of ovarian denervation on hormone levels depends on which ovary is preserved [12, 13]. In particular, when the left ovary was sacrificed, the right ovary was found to secrete higher levels of estradiol (E2) compared to the contralateral ovary, whereas in cases of right UO, the remaining left ovary was associated with higher FSH serum level concentrations. Progesterone level concentrations, on the contrary, did not appear to be influenced by the side where oophorectomy was performed [12].

Specifically differentiating between right and left-ovariectomized animals, a previously published study carried out on squirrels showed that unilaterally ovariectomized individuals did not experience any significant difference in terms of reproductive time span and outcome, compared to the control groups [14]. On the contrary, during lactation, estradiol and progesterone serum levels were, respectively, higher and lower in squirrels with one ovary [14]. These observations confirm that a compensatory phenomenon occurs in the remaining ovary, and the higher serum estradiol level might be preventing excessive follicular compensation. Recently, a very interesting insight into adult birds with one and two ovaries and oviducts, was published, raising important and provocative questions about this issue [15].

Unilateral oophorectomy in women

In humans, it is well established that bilateral oophorectomy performed for preventive or curative reasons before the onset of menopause negatively affects women's overall health. Negative sequelae include an increased risk over time of cardiovascular [2] and neurological diseases [3], mental disorders [5] and overall mortality [6].

Although a compensatory increase in contralateral ovarian volume has been observed in unilaterally oophorectomized young women [16], the biological effects occurring after UO still remain unclear. Theoretically, if compensatory mechanisms kick in after UO, few or no effects should be expected. However, several questions still remain unanswered:

1. Is age at onset of menopause affected by UO?
2. Does the increased risk of cardiovascular and neurological diseases recorded for patients with bilateral oophorectomy apply to women who have undergone UO as well?
3. Does UO increase the risk of mortality in the same way that bilateral oophorectomy does?
4. Are the consequences, if any, of UO the same, regardless of laterality?
5. What is the impact, if any, of UO on fertility outcome?
6. Is there really a clinical difference between ovarian cystectomy and UO?

Unilateral oophorectomy and onset of menopause

Where the removal of one ovary influences the onset of menopause in patients who are of reproductive age is still the subject of investigations. In Norway, a survey of 23 580 women (the HUNT2 survey) revealed that women who had undergone UO experienced the onset of menopause one year earlier compared to women who did not (49.6 vs. 50.7 years, $p < 0.001$) [17]. This difference remained significant even after adjustment for birth cohort, parity, smoking, body mass index (BMI) and age at menarche. Although significant, this difference is small, considering that ovariectomized women were deprived of half of their follicular reserve. These results are consistent with those of a large cohort study of 24 252 Japanese women that showed an earlier onset of menopause in women who had undergone UO (50.9 vs. 52.1 years, HR 1.40, 95% CI: 1.22–1.60) [18].

More recently, Rosendahl et al. [19] came to the same conclusions, after demonstrating in a large cohort of 17 781 Danish women that UO significantly reduces the age at onset of menopause by 1.8 years (mean 49.5 vs. 51.3 years). Furthermore, they found that younger age at UO was significantly linearly correlated to younger age at menopause.

The data in the literature are coherent in showing that onset of menopause occurs slightly earlier, suggesting that some compensatory mechanism takes place.

Unilateral oophorectomy and risk of cardiovascular and neurological disorders

Only one previous cohort study with long-term follow-up, which included 4784 women and was published 10 years ago, investigated the differences with respect to cardiovascular risk between bilateral and unilateral oophorectomy [20]. Interestingly, whereas bilateral oophorectomy increased the incidence of cardiovascular events and its correlated deaths, UO conferred some protection: women who had undergone UO had a reduced mortality associated with cardiovascular disease compared to women who had both ovaries removed (HR 0.82; 95% CI: 0.67–0.99; $p = 0.04$). Although this data was both strong and surprising, the authors offered no biological reasons in support, and it needs to be confirmed by subsequent large cohort studies.

Epidemiologic studies performed at the Mayo Clinic showed that women undergoing UO before the onset of menopause have an increased risk of cognitive impairment, dementia and Parkinson disease compared to women who still have both ovaries [21, 22]. This risk seems to be of comparable magnitude to that recorded in patients who have undergone bilateral oophorectomy [21, 22]. These data have been confirmed by Zhou et al., who showed deleterious long-term effects on cognitive function in women who underwent UO [23].

Unilateral oophorectomy and mortality risk

Data on mortality after UO are somewhat controversial. Unlike patients who undergo bilateral oophorectomy, patients with UO do not seem to have an increased mortality risk [6]. In a larger cohort of patients, the same group of researchers reported an increased overall mortality risk in patients who undergo UO before the age of 45 without concurrent hysterectomy [3]. Unlike the data recorded in the same study for patients who had undergone a bilat-

eral oophorectomy, this increase in mortality was not related to neurological or mental disorders and the explanation remains unclear. Interestingly, considering the causal relationship between UO and women's mortality, Rice et al. [24] found, in a large cohort of unilaterally oophorectomized women, a 30% reduced risk (HR 0.70, 95% CI: 0.53–0.91) of developing future ovarian cancer comparing to non-oophorectomized women, irrespective of the histological cancer subtype.

Laterality of unilateral oophorectomy

Interestingly, medically indicated unilateral oophorectomies are more commonly performed on the left side, probably secondary to the higher prevalence of endometriosis [1]. To the best of our knowledge, the effects of laterality of UO have not been investigated yet in the human setting.

Unilateral oophorectomy and spontaneous fertility

Curiously, little has been written on the effects of UO on the reproductive potential of women. In a retrospective study published

in 2014, the postoperative reproductive outcome after UO was compared to that of other abdominal non-gynecological procedures such as appendectomy (AP) and cholecystectomy (CO) [25]. All surgeries were performed for benign indications. No significant differences in terms of pregnancy rates, “take home baby” rates and miscarriage rates were observed between the three groups. In particular, the rate of women who had at least one successful postoperative pregnancy was 48.5% in ovariectomized patients, 41% in patients who had appendectomy, and 53.8% in women treated with cholecystectomy (UO vs. AP, $p = 0.55$; UO vs. CO, $p = 0.99$; AP vs. CO, $p = 0.53$). Large prospective studies comparing fertility outcomes between unilaterally ovariectomized women and women with two healthy ovaries are still needed.

Unilateral oophorectomy and ART (assisted reproductive technology)

Twenty-two studies were identified which reported on ART outcomes after UO [26–45] (► **Table 1**). Assisted reproductive tech-

► **Table 1** Studies comparing fertility outcomes in women undergoing ART with or without previous unilateral oophorectomy.

First author	Type of study	No. of patients with UO/total no. of pts.	Indication for UO no. (%)	Indication for ART no. (%)
Diamond 1984	Cohort study	38/117	N.A.	N.A.
Alper 1985	Cohort study	14/28	Ectopic pregnancy 5 (36)	Endometriosis 6 (21.5)
			Ovarian cyst 2 (14)	Ectopic pregnancy 6 (21.5)
			Endometriosis 1 (7)	PID 12 (43)
			PID 2 (14)	Unexplained infertility 4 (14)
			Unknown 4 (29)	
Dodds 1987	Cohort study	16/34	Ectopic pregnancy 3 (19)	Endometriosis 6 (17.65)
			Ovarian cyst 1 (6)	Adhesions 12 (35.29)
			Endometriosis 5 (31)	Tubal occlusion 16 (47.05)
			PID 3 (19)	
			Adhesions 3 (19)	
			Congenital absence 1 (6)	
Boutteville 1987	Cohort study	86/501	N.A.	N.A.
Dodson 1987	Cohort study	ND/ND	N.A.	N.A.
Alper 1987	Cohort study	10/18	N.A.	N.A.
Lam 1987	Cohort study	34/369	N.A.	N.A.
Horsnstein 1989	Cohort study	6/69	Ectopic pregnancy 1 (16.7)	Endometriosis 5 (7.2)
			Ovarian cyst 1 (16.7)	Tubal occlusion 41 (59.4)
			Endometriosis 2 (33)	Unexplained infertility 6 (8.7)
			PID 1 (16.7)	Multiple causes 10 (14.5)
			Congenital absence 1 (16.7)	Miscellaneous 3 (5)
Pampfer 1989	Cohort study	8/18	N.A.	N.A.
Khalifa 1992	Cohort study	135/ND	Ectopic pregnancy 23 (15)	N.A.
			Ovarian cyst 24 (15.7)	
			Endometriosis 72 (47)	
			PID 34 (22.3)	

Continued next page

► **Table 1** Studies comparing fertility outcomes in women undergoing ART with or without previous unilateral oophorectomy. (Continued)

First author	Type of study	No. of patients with UO/total no. of pts.	Indication for UO no. (%)	Indication for ART no. (%)
Penzias 1993	Cohort study	7/91	N.A.	Endometriosis 7 (7.7)
				Tubal occlusion 54 (59.3)
				Male factor 12 (13.1)
				Diethylstilbestrol exposure 2 (2)
				Unexplained infertility 15 (16.4)
				Anovulation 1 (1)
Nargund 1995	Case control	17/39	Ectopic pregnancy 2 (12)	Tubal occlusion 44 (100)
			Ovarian cyst 11 (64.5)	N.A.
			PID 4 (23.5)	N.A.
Lass 1997	Case control	58/939	N.A.	N.A.
Levitas 2000	Case control	10/57	N.A.	Tubal occlusion 57 (100)
Levi 2003	Case control	ND/ND	N.A.	N.A.
Al Hasani 2003	Case control	24/133	Ectopic pregnancy 3 (12.5)	Male factors 133 (100)
			Ovarian cyst 11 (46)	N.A.
			Endometriosis 10 (41.5)	N.A.
Asimakopoulos 2003	Case control	7/38	N.A.	N.A.
Esinler 2006	Case control	19/64	N.A.	N.A.
Hendricks 2010	Cohort study	18/62	N.A.	N.A.
Khan 2014	Cohort study	51/153	Ectopic pregnancy 5 (10)	Endometriosis 18 (11.7)
			Ovarian cyst 17 (33)	Tubal occlusion 49 (32)
			Endometriosis 13 (26)	Male factors 4 (8.3)
			PID 2 (4)	Unexplained infertility 45 (29.4)
			Ovarian torsion 6 (11)	Anovulation 21 (13.7)
			Pelvic pain 3 (6)	Unexplained infertility 20 (13.07)
			Benign tumor 2 (4)	N.A.
			Malformation 3 (6)	N.A.
Wilkosz 2014	Cohort study	97/6844	Ectopic pregnancy 7 (7.2)	Endometriosis 1496 (21.8)
			Ovarian cyst 23 (23.7)	Tubal occlusion 1603 (23.4)
			Endometriosis 21 (21.6)	Male factor 2699 (39.4)
			PID 8 (8.2)	Unexplained infertility 1582 (23.11)
			Benign tumor 2 (4)	Multiple causes 364 (5.31)
			Borderline/malignant tumor 7 (7.2)	N.A.
			Unknown 12 (132.4)	
Lind 2018	Cohort study	154/22847	N.A.	Tubal factor 3925 (17)
				Anovulation 3679 (16)
				Endometriosis 2402 (10.5)
				Ovarian 1516 (6.6)
				Uterine/cervical cancer 68 (0.3)
				Male factors 9125 (39.9)
				Unexplained 13 655 (59.7)
				Unspecified diagnosis 7196 (31)

UO: unilateral oophorectomy; ART: assisted reproductive technology; N.A.: not available; PID: pelvic inflammatory disease

nology (ART) outcomes after UO have been investigated in various studies with conflicting results. The majority of the series reported similar pregnancy rates between women who had undergone UO compared to women requiring ART who had both ovaries [26–36]. Other series have shown better results in patients who underwent UO, with one series reporting better pregnancy rates in women with both ovaries [37–38,45]. A recent meta-analysis of controlled studies comparing infertile women after UO with women with two intact ovaries undergoing ART revealed an adverse effect of UO on ovarian reserve, which affected the quantity but not the quality of the ovarian pool [46].

After this publication, a multicenter cohort study was recently published [47,48], comparing 154 UO women with 22693 controls. It revealed lower live birth rates after IVF/ICSI in women with previous UO. The difference was significant in terms of live birth rates per started cycle (18.6 vs. 25.4%, $p=0.007$ crude and $p=0.014$ adjusted), per ovum pick-up (20.3 vs. 27.1%, $p=0.012$ crude and $p=0.015$ adjusted) and per embryo transfer (23.0 vs. 29.7%, $p=0.022$ crude and $p=0.025$ adjusted), for both fresh and frozen-thawed transfers. The results contradicted those of previously published studies of the last 30 years. Nevertheless, this study includes the largest sample size of women with UO ($n=154$) who underwent 301 IVF/ICSI cycles, which offered the high statistical power required to analyze live birth rate differences as a primary outcome. Although many patients in the UO group had endometriosis, thus including a potential selection bias for the presence of a poorer fertility factor in the UO group, adjustment for all known confounders did not affect the overall results. Moreover, the US national data report showed that only when endometriosis was associated with a concomitant diagnosis was the live birth rate affected [49]. In addition, the number of retrieved oocytes, embryos with a good quality morphology, and the ratio between oocyte yield and FSH score (ovarian sensitivity index) were all significantly lower in the OU group, further supporting the idea that there is both a quantitative and qualitative reduction of ovarian reserve in this patient group, decreasing the pregnancy rate. Further studies will be necessary to better clarify these contradictions and to understand the real clinical effect of UO on live birth rate in IVF/ICSI patients.

► **Table 1** reports all the indications for ART and UO of patients enrolled in the studies and compares fertility outcomes of women undergoing ART with or without previous unilateral oophorectomy.

Unilateral oophorectomy versus cystectomy

When treating an adnexal mass in a woman of reproductive age, an ovarian cystectomy is usually attempted to preserve as much ovarian parenchyma as possible. However, depending on the size of the mass which may occupy the site of entire ovary or in cases of suspicion of malignancy, an oophorectomy may be required in some cases.

Sometimes, very little parenchyma is left. It is unclear if an ovarian remnant may significantly contribute to the endocrine and reproductive function of the individual or whether this condition is more similar to that of women who have undergone UO.

A small prospective study of 50 patients undergoing unilateral or bilateral ovarian cystectomy for various benign conditions

showed significantly decreased postoperative AMH serum levels at one and three months, suggesting a diminished ovarian reserve even after cystectomy [50]. This was true for endometriomas and other benign cysts and for unilateral and bilateral cystectomy. A similar prospective trial of seventy patients undergoing laparoscopic ovarian cystectomy for endometriomas and other benign ovarian cysts confirmed a short-term significant decline in ovarian reserve markers that disappeared at 6 and 12 months after the surgery, suggesting a compensatory effect of the remaining parenchyma and contralateral ovary [51]. In a recent meta-analysis on borderline ovarian tumors, no differences in oncologic outcome and pregnancy rates were recorded in women undergoing ovarian cystectomy compared to those undergoing UO [52]. In cases with borderline tumor of serous histology, ovarian cystectomy is recommended to preserve fertility despite the higher local recurrence rate, because of the high bilateral involvement associated with the disease.

Conclusions

In conclusion, certain compensatory mechanisms from the contralateral ovary that are not yet understood kick in in women who undergo UO. As a result, the age at onset of menopause of women with two ovaries differs by approximately one year from the age at onset of menopause of women who have undergone UO. However, the spontaneous reproductive potential of patients who have undergone UO seems to be similar to that of women who still have two ovaries, whereas UO has been recently associated with reduced live birth rates after IVF/ICSI techniques.

Interestingly, the compensatory mechanisms involving the contralateral ovary may not be sufficient to prevent an increased risk of neurological disease and even an increased mortality risk. These data need to be confirmed by further studies, and the plausible mechanisms of action need to be identified. At present, patients who undergo UO can be reassured with regard to their reproductive potential and their age at onset of menopause.

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Authors' Contribution

- Conception of the work: DC and FB
- Design of the work: MLG and IR
- Acquisition of data: LT, FC, MPDM, EIB
- Analysis and interpretation of data: MLG, IR, JS, MDM, AP, DC, FB
- Drafting the final manuscript: All co-authors
- Critical revision of the final version of the manuscript before submission: All co-authors

Conflict of Interest

The authors declare that they have no conflict of interest.

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