Bone Loss After Hysterectomy Despite Ovarian Conservation

Estimated by a new specific marker Urinary Deoxypyridinoline

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M.D. Degree in Obstetrics and Gynaecology

by

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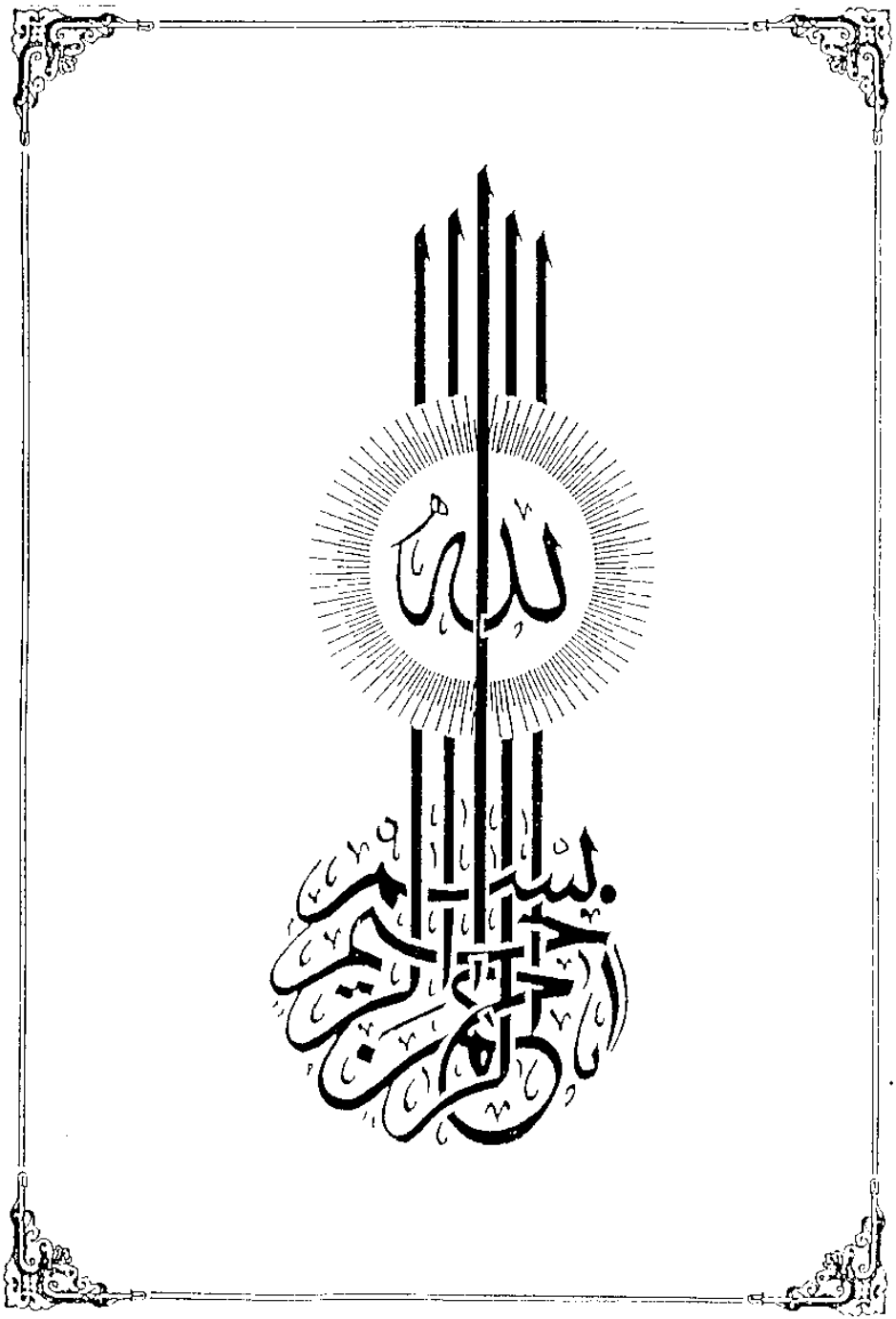


بسم الله الرحمن الرحيم

وقل ربي زدني علماً

CONTENTS

1. WHY STUDY OVARIAN FUNCTION AFTER HYSTERECTOMY

1.1. The consequences of premature ovarian failure

The central issue is the possibility that hysterectomy may cure a gynaecological problem but may cause the unwanted adverse consequences of ovarian failure and oestrogen deficiency to occur at an earlier age than would normally be the case. The problems that are *natural* at 50 - 51 years of age seem out of context and outside expectation when they happen years earlier.

What are these adverse consequences? The symptoms of ovarian failure are hot flushes, vaginal dryness, dysphoria and sleep disturbance. The signs of oestrogen lack are such bodily changes as thinning of skin, thinning and dryness of the vagina, loss of hair and eventually reduction in bone mass. The associated dysfunctions eg psychological: poor memory and reduced confidence; sexual: loss of libido poor vaginal lubrication and diminished capacity for orgasm and urinary: urgency and frequency of micturition, are disabling in young women. Finally, it is established that women with premature ovarian failure [POF] have an increased incidence of potentially fatal myocardial infarction. If there is POF after hysterectomy this amounts to an advancement of the ageing process and a significant alteration in quality of life.

If hysterectomy has these consequences, then women are right to have been wary of the increasing rate of hysterectomy in western society. More scientifically, if hysterectomy causes these problems at an unacceptably early age then this is a vitally important area of study so that we may understand the problem and take steps to manage it appropriately. Awareness and early intervention can limit the adverse consequences.

1.2. An unanswered question: the published data is inconclusive

The effect of hysterectomy on ovarian function is an area of controversy. The published data is contradictory and inconclusive [see section 2.2 below]. These studies have not looked reliably at ovarian function. In part this is because there have been few modern studies. It is also, in part because of a poor understanding by some investigators of the endocrinology of ovarian failure and in part because the endpoints chosen [such as single point measurements of gonadotrophins] are imprecise. Only a small number of studies have looked at the finite consequences of ovarian failure after hysterectomy for example effects on bone density or bone turnover. This area is therefore ripe for further study in order to answer reliably the question "does hysterectomy affect the function of ovaries conserved at operation".

1.3. To facilitate informed consent

Current thinking is that patients must be fully aware of the consequences of surgery before it can proceed. If hysterectomy has no effect on the age of ovarian failure then this is not an important issue in preoperative counselling. If however women who undergo hysterectomy will experience significant changes in the quality and quantity of ovarian sex steroid secretion, then this is a matter for full discussion before the patient can consent.

1.4. Conclusion

The fate of ovarian function after hysterectomy is therefore an interesting and important scientific issue: moreover, existing data does not answer all the questions. The effect of hysterectomy on ovarian function has important implications for both surgeon and patient. It is therefore essential that preoperative counselling deal with this issue comprehensively and accurately. We urgently need good quality data to guide the gynaecologist and fully inform the patient.

2. THE HISTORY OF POST-HYSTERECTOMY STUDIES

2.1. Overview

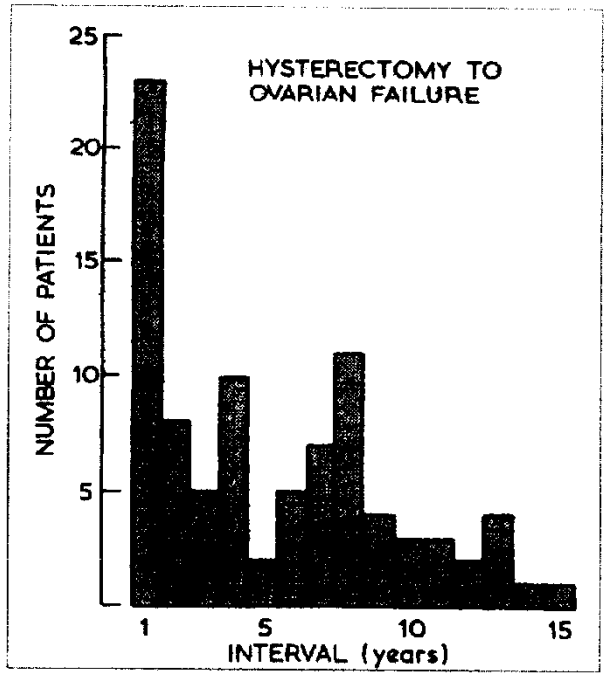
The early history of this subject is intertwined with a separate and distinct clinical question that has preoccupied gynaecologists for over thirty years. This separate but related controversy is whether the gynaecologist should remove or conserve the ovaries in a premenopausal woman undergoing hysterectomy. This subject has aroused passionately held views and led to papers written to support both sides of the argument. In other words whether to conserve ovaries and preserve functionality or remove them prophylactically to prevent the possibility of later ovarian cancer. The data that is available on postoperative ovarian function is often hidden in a paper that has been written to support one or other side of this argument rather than to study the effect of hysterectomy on ovarian function.

The first paper to look critically at this question in recent times was the publication by Siddle, Sarrell and Whitehead in 1986[1]. These authors looked at a group of menopause clinic patients and compared 90 who had undergone hysterectomy with controls from the clinic population. They used strict criteria for inclusion and timing of "ovarian failure" although they accepted that the population was highly selected and that the data, collected retrospectively, was incomplete.

When Siddle et al analysed the data the mean age of ovarian failure was ~ five years earlier in the hysterectomised group. There were significant numbers of women < 45 years at operation who had experienced ovarian failure within two years of operation.

These authors looked at previous publications and discovered a "hidden" incidence of this problem ranging from 16-57%. The interval from operation to adjudged ovarian failure is shown below.

Figure 1: The time of onset of ovarian failure [from Siddle et al]



Around 46% of patients had become menopausal at 5 years. Subsequently several authors have recognised that the function of ovaries after hysterectomy should be specifically studied and have tried to study this using modern methodology. There have also been studies looking at practically important endpoints such as bone mass. These are discussed later.

2.2. The Published Data

2.2.1. *Early studies 1932-1977*

The early studies that are included here are those that present data that showed, directly or indirectly, the percentage of women that go on to develop premature ovarian failure [% POF].

Table 1: The early studies 1932-1977

Authors	Year	Nos patient	Years followed	% early ovarian failure [POF]
Sessums & Murphy[2]	1932	37	1-14	32.4
Kretzschmar & Gardiner[3]	1935	64	1-30	57.5
Dippel[4]	1939	42	1-8	17
Richards[5]	1951	204	2-6	27
Bancroft-Livingstone[6]	1954	353	2-12	32
Grogan & Duncan[7]	1955	363	1-6	14.6
Randall et al[8]	1957	47	5-10	23
Whitelaw[9]	1958	24	2-8	25
Leverton[10]	1958	144	7	20
De Neef & Hollenback[11]	1966	115	1-20	35.6
Beavis et al[12]	1969	48	1-14	16.7
Ranney & Abu Ghazaleh[13]	1977	59	1-20	23

2.2.2. *Comments on the historical studies*

The information on the percentage of women experiencing ovarian failure after hysterectomy was obtained from careful scrutiny of the authors' data. The information is not always specifically reported as this was not the principle reason for study in these early reports. Indeed Siddle et al[1] noted that the authors often omitted to mention or ignored the significant percentage of women who had post-hysterectomy ovarian failure. In many cases, some remark such as *"In the majority ovarian function was unaffected"* was the only comment on the data.

It must be recognised that the methodology was haphazard and imperfect. The best measures of failed ovarian function in these early studies were the presence of hot flushes or vaginal dryness, identified retrospectively: although two of the studies shown in the table used gonadotrophin assays. Having said this, consistent hot flushes that are present for several months correlate well with low oestradiol production. They do not necessarily reflect total failure of ovarian follicular output. Symptoms occur before ovarian failure. Consistently raised ie menopausal-range gonadotrophins are better [*see section 4.4, below*]. Furthermore, symptoms provide an imperfect index of the time of ovarian failure.

The purpose of reviewing these early studies is to support the hypothesis that ovarian function after hysterectomy is a subject that is worthy of investigation. In reviewing the early studies, Siddle et al[1] commented.

> *Despite these limitations, our finding that a subgroup of women developed ovarian failure at an early age following hysterectomy is supported by the medical literature. The major studies of ovarian function following hysterectomy published during the last 50 years from which numerical data can be extracted are shown in the Table. We have extracted the numbers of women with unilateral or bilateral ovarian conservation who were < 45 years at the time of operation, and the numbers subsequently developing ovarian failure according to the authors' criteria. These have varied from the presence of hot flushes alone to the use of vaginal smears, and most recently, biochemical methodology. In the majority of cases, we have selected the figures relating to women with flushes. Because details of the time of assessment of individual women are only available in two papers, more detailed analyses are not possible. However, all the authors reported a sub-group of women with premature ovarian failure, the percentage ranging from 16.7% to 57.5% (mean, 23.5% ± 5.3%). Most authors ignored this subgroup.*
>
> *For example, Whitelaw, using measurements of urinary pregnanediol and a bioassay to determine gonadotrophin activity, concluded that "continued ovarian activity is manifest in the majority of these subjects years after operation." However, "the majority" in this study means 18 of 24 women, because in the other 6 subjects the author stated "menopause was probably reached." Beavis et al. used*

symptomatic assessments and serial urinary estrogen and pregnanediol measurements as indicators of ovarian activity. They concluded, "ovarian function continued normally up to the time of the menopause." Our understanding of their data is that 16.7% of women experienced premature loss of ovarian function.

Ranney and Abu-Ghazaleh relied solely on the presence of symptoms to assess ovarian function. Their study group was 1263 women. The authors concluded, "normal ovaries which are retained in vivo during hysterectomy will usually produce female hormones in each individual patient for the inherited duration of years." However, careful examination of the authors' scatter-grams for the 59 women who were <40 years old at the time of surgery indicates that 23% of this group experienced loss of ovarian function prematurely.

The most recent prospective study of which we are aware is ongoing at Oxford and is an investigation of the psychiatric sequelae of hysterectomy. Professor Gath has kindly reviewed his data for us and reports the following among women under the age of 44 years at the time of hysterectomy in whom the ovaries were conserved. Within 6 months of surgery, 17.6% of the women were experiencing hot flushes and 24.3% had sweating. Eighteen months after operation, hot flushes were reported by 19.5% and sweating by 18.5% of patients. Four years after operation, 24.6% of women experienced hot flushes and 28.1% had sweating; 25% of the women also reported vaginal dryness.

Comparisons between the above studies are, we believe, inappropriate because of differences in study design, inclusion criteria, and length of follow-up. Nonetheless, it is clear that in each reported series some women have experienced premature ovarian failure following hysterectomy.

The body of published evidence supports the view that hysterectomy affects ovarian function. The reasons for this premature decline in ovarian function are not clear and the methodology of the early studies is rather poor. However further investigation seems necessary.

2.2.3. *Studies of possible mechanisms*

The five studies in this table are of interest as one-off studies of specific issues relating to ways in which hysterectomy might affect the ovary.

Table 2: Studies of possible mechanisms

Authors	Year	Comments
Sessums and Murphy[14]	1933	Rabbit study; effect of endometrium.
Johansson BW et al[15]	1975	Various effects of hysterectomy.
Stone SC, Dickey RP, Mickal A[16]	1975	Pre and postoperative E2 level.
Janson PO, Jansson[17]	1977	Xenon clearance study.
Cattanach[18]	1985	Study of tubal ligation: hypothesis of vascular impairments.
Souza et al[19]	1986	Histological study of ovarian biopsies.

Sessums and Murphy[20] demonstrated that the presence of uterine tissue is important for normal ovarian follicular development in rabbits. In elegant studies of animals that had undergone hysterectomy 12 months previously they showed that there were only half the number of follicles expected, compared with rabbits with intact uteri. When endometrium had been implanted into the anterior abdominal wall of rabbits that had undergone hysterectomy, this effect was reversed and there were 40% more follicles than in the hysterectomised group. This implies that some factor in the endometrium is important for normal follicular development.

It is difficult to extrapolate this to *Homo sapiens* as there is currently no data that shows any uterine humoral factor that is necessary for ovarian function. The possibility of an important local growth factor must not, however, be dismissed.