A randomised controlled trial comparing surgical intervention rates between two protocols for the management of asymptomatic adnexal tumours in postmenopausal women

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ABSTRACT

Introduction: Detection of asymptomatic adnexal tumours in postmenopausal women has increased due to wider use of diagnostic ultrasound and imaging quality improvements. Reliable methods to differentiate between benign and malignant tumours are required to avoid delays in treating ovarian cancer and to prevent unnecessary interventions for benign lesions. In the UK, the Royal College of Obstetricians and Gynaecologists has issued guidance for the management of adnexal cysts in postmenopausal women, which is considered standard in routine clinical practice. The protocol utilises the Risk of Malignancy Index to assess the risk of adnexal lesion being malignant. This protocol has a relatively high intervention rate in order to avoid a delay in a cancer diagnosis. The Simple Rules Protocol designed by International Ovarian Tumour Analysis Group reports a low false-positive rate in the diagnosis of ovarian cancer without a loss of sensitivity and therefore has the potential to reduce unnecessary interventions in asymptomatic postmenopausal women with benign cysts.

Methods and analysis: 140 postmenopausal women aged 40–80, with incidentally detected adnexal tumours on ultrasound scan will be recruited to this study. They will be randomly allocated, to be assessed and managed according to either of the two protocols under investigation. In both arms of the study the tumours will be classified into three groups: high, intermediate or low risk of malignancy. Women with high risk of malignancy will be referred for management in a tertiary cancer centre, women with low-risk tumours will be managed expectantly, while those with intermediate risk findings have surgery in their local hospital units. Analysis will be on an intention-to-treat basis.

Ethics and dissemination: Research ethical approval was granted by the North London Research Ethics Committee 2 (10/H0724/48). Trial results will be published according to the CONSORT statement.

ARTICLE SUMMARY

Article focus

- The primary objective is to assess the differences in surgical intervention rates between two different protocols for the management of incidentally detected adnexal tumours in postmenopausal women.
- Assessment of adnexal tumours using the Risk of Malignancy Index (RMI) calculation alongside the guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) as compared with the Simple Rules as designed by the International Ovarian Tumour Analysis Group.

Key messages

- Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm.
- A test, which can better discriminate between benign and malignant tumours will afford women without a malignancy to decline surgery.

Strengths and limitations of this study

- This is the first randomised controlled trial to assess the RMI and the RCOG protocol against the Simple Rules protocol for the management of asymptomatic adnexal tumours in postmenopausal women.
- It is a single centre study, which can affect the applicability of the results in other units.
- Both assessment and management protocols have high sensitivity rates with low false-negative rates.

INTRODUCTION

Wider and more liberal use of diagnostic ultrasound in gynaecological clinics has resulted in the detection of adnexal tumours in a large number of asymptomatic postmenopausal women. There has also been an increase in the use of other imaging modalities such as CT and MRI to assess a variety of...
medical complaints resulting in incidental detection of adnexal tumours. Any adnexal cyst detected in meno-
pause has a potential of being malignant.

In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) has issued a guideline for the
management of cysts in postmenopausal women, which is widely used in the routine clinical practice.1
According to this protocol all adnexal cysts/tumours are categorised as high, intermediate and low risk of being
malignant. This categorisation is based on the Risk of Malignancy Index (RMI) calculation.2 This model calcu-
lates a score which is the product of the value of the CA 125 (U/ml), a score for menopausal status (1 if preme-
nopausal and 3 if postmenopausal) and a greyscale ultra-
sound score of 0, 1 or 3 where 1 score is given each for
bilaterality, ascites, multilocular, solid areas and intra-abdominal metastases. In the original study by
Jacobs, a score of >200 gave a sensitivity of 85% and a
speciﬁcity of 97% for the diagnosis of ovarian cancer. A recent systematic review of 16 studies assessing the
diagnostic performance of RMI showed that the test had
an overall sensitivity of 78% (95% CI 71% to 85%) and
a speciﬁcity of 87% (95% CI 83% to 91%).3

The RMI has the advantage of being simple and widely
used. Its disadvantage though is that it includes a blood
test for CA125, which adds to the cost. In addition the
diagnosis is delayed until the result of blood test is avail-
able. The absolute value of the RMI and the level of
CA125 in serum are used to determine the management
plan. Simple unilateral adnexal cysts of <5 cm with an
RMI of <25 and where the CA 125 is < 30 μ/ml are con-
sidered low risk. For cysts with an RMI ≥25 but where the
CA 125≥30 μ/ml, the cyst is ≥5 cm or the cyst has septa-
tions or solid areas then these are considered of inter-
mediate risk. Those with an RMI of 25–250 are also
considered to be of indeterminate risk. Adnexal tumours
with an RMI >250 are classiﬁed as high risk.1 (Flowchart)
As the main aim of this protocol is to minimise the risk of
delaying interventions in women with ovarian cancer, the
overall intervention rates are relatively high and many
women with benign lesions are treated by surgery.

In recent years, the International Ovarian Tumour
Analysis (IOTA) collaboration has developed several
novel diagnostic models with the aim of improving non-
invasive diagnosis of ovarian cancer. In 2008, the collab-
oration proposed use of ‘Simple Rules’ to assess
tumours.4 The ‘Simple Rules’ are based on a structured
approach to morphological analysis of ovarian tumours
on ultrasound scan. It enables discrimination between
benign and malignant lesions without the need to
measure tumour markers.

Ultrasound scan ‘Simple Rules’ use 10 rules to assess
adnexal tumours. There are ﬁve rules to predict malign-
ancy (M-rules): (1) irregular solid tumour; (2) presence
of ascites; (3) at least four papillary structures; (4) irregu-
lar multilocular–solid tumour with a largest diameter of
at least 100 mm and (5) very high colour content on
colour Doppler examination (colour score 4). There are
five rules to suggest a benign tumour (B-rules): (1) uni-
locular cyst; (2) the presence of solid components
where the largest solid component is <7 mm in largest
diameter; (3) acoustic shadows; (4) smooth multilocular
tumour less than 100 mm in largest diameter and (5) no
detectable blood flow on Doppler examination (colour
score 1).

If one or more M-rules apply in the absence of a
B-rule, the mass is classiﬁed as malignant. If one or
more B-rules apply in the absence of an M-rule, the
mass is classiﬁed as benign. If no rule applies or both M
and B rules apply, the mass cannot be classiﬁed and
deﬁned as indeterminate.

Inclusion criteria

All postmenopausal women aged 40–80 who are referred
for an asymptomatic adnexal tumour or those found
to have one at the time of their visit to the gynaecology
unit will be invited to take part of the study. Postmenopausal women are deﬁned as those who have
had 1 year of spontaneous amenorrhoea at or above the
age of 40 where no illness or medication may have


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caused the amenorrhoea or those at or above the age of 50 who have had a hysterectomy. Women will be judged to be asymptomatic if they did not present with pain localised to the area of the tumour or the lower pelvis.

Women who present with pelvic pain that could be attributed to the tumour and those who are younger than 40 or older than 80 years of age will be excluded. Women who are unable to consent and those with simple unilateral unilocular cysts <2 cm in size will also be excluded as the RCOG guideline stipulates these women do not require follow-up.

Interventions
All women will have an initial ultrasound scan. All examinations will be performed by level II ultrasound operators, who have been fully trained in the assessment of adnexal tumours using both the RMI and ‘Simple Rules’ approach. Those randomised to the RCOG/RMI group will also have a blood test taken for the measurement of serum CA125. The tumours will be classified as low, intermediate and high risk as previously described (flowchart). In the Simple Rules group, adnexal tumours will be classified as low risk if one or more B-rules apply in the absence of an M-rule. If one or more M-rules apply in the absence of a B-rule, the mass will be classified as high risk. If no rules apply or if both M and B rules apply, the tumour will be classified as intermediate risk.

Women with tumours classified as high risk of malignancy by either protocol will be referred to the Gynaecological Oncology team. Tumours found to be of intermediate risk will be offered surgery by the general gynaecology team. All asymptomatic women diagnosed with low-risk tumours will be managed conservatively and have 4 monthly scans for 1 year observing for any changes in the tumour size or morphology. Should the characteristics of the tumour change prompting its classification into intermediate or high-risk category, the management plan will be modified accordingly.

Outcome measures
The primary outcome is the rate of surgical intervention. Secondary outcomes include the number of delayed diagnoses of ovarian cancer, number of staging surgical procedures and number of surgical complications.

Randomisation
A statistician using a Stata V.12.1 (Stata Corp., College Station, Texas, USA) will generate the blocked randomisation list with varying block sizes. The randomisation numbers will be placed in sealed, opaque, numbered envelopes and kept in a locked in a filing cabinet. This randomisation ensures allocation concealment. When a patient consents, a clinic nurse who is not part of the research team will access the next envelope and give it to the recruiting doctor.

DISCUSSION
Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm.

By avoiding surgery women are not exposed to surgical and anaesthetic complications and their care is likely to be more cost effective. Recent trials have shown that unnecessary interventions in women with benign adnexal lesions lead to significant morbidity and mortality, which offsets the potential benefits of screening for ovarian cancers. Postmenopausal women are also more likely to suffer from chronic medical problems such as diabetes and high blood pressure, which increase operative and anaesthetic risks. Women with presumed benign cysts will be observed over the following year in 3–4 monthly intervals in order to detect any change in

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appearance or increase in size, which would be suspicious of malignancy. Any suspicion of malignant change would trigger a surgical intervention.

We will record sensitivities of both protocols for the detection of ovarian cancer. Although our audit showed that all cases of ovarian malignancies were correctly classified by both protocols, it is important to confirm this observation in a larger prospective study. We do expect, however, that the specificity of the ‘Simple Rules’ protocol will be higher, which should translate into lower intervention rates.

If the study shows that the use of the ‘Simple Rules’ and conservative management could substantially reduce intervention rates without increasing the risk of delaying the diagnosis of ovarian cancer this could have a positive impact on clinical practice, increase patients’ safety and result in significant savings for the health services.

Ethics and dissemination

Approval for this study was obtained from the North London Research Ethical Committee 2 (North REC 2), London, UK (10/H0724/48). Written informed consent is obtained from each patient fulfilling the inclusion criteria before randomisation. Women who refuse participation are recorded. There is a small risk to patients of a delayed diagnosis of ovarian cancer and there are also the risks of surgery for those who are offered surgical intervention.

Incident reporting

Adverse events will be recorded from recruitment to the 1-year-scan date for those who have conservative management or to 3 months postoperatively for those who have surgery. The chief investigator will be responsible for the reporting of all serious adverse events or suspected unexpected serious adverse reactions immediately or as soon as the trial personnel become aware of an event. The chief investigator will report all fatal or life-threatening events as soon as possible to the trial coordinating centre. This will be done not later than 7 days after the chief investigator is first aware of the event. All events which are not fatal or life-threatening will also be reported as soon as possible and not later than 15 days after the chief investigator is first aware of the reaction. The research and ethics committee also require a report of all SAEs and SUSARs within 15 days of the chief investigator being made aware. The principal investigator will also follow all SAEs and SUSARs through to outcome.

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REFERENCES

1. RCOG Ovarian cysts in postmenopausal women Guideline No. 34 October 2003.
2. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97:922–9.
3. Geomini P, Kruitwagen R, Bremer GL, et al. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstet Gynecol 2009;113(2 Pt 1):384–94.
4. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol 2008;31:681–90.
5. Timmerman D, Ameye L, Fischerova D, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses prior to surgery: a prospective validation by the IOTA group. BMJ 2010;341:c6819.
6. Di Legge A, Testa AC, Ameye L, et al. Lesion size affects diagnostic performance of IOTA logistic regression models, IOTA simple rules and risk of malignancy index in discriminating between benign and malignant adnexal masses. Ultrasound Obstet Gynecol 2012;40:345–54.
7. Machin D, Campbell MJ, Tan SB, et al. Sample size tables for clinical studies. Comparing paired groups of binary, ordered categorical and continuous outcomes. Oxford, UK: Wiley-Blackwell, Third 2009, 69–83.
8. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial. JAMA 2011;305:2295–303.