Protocol for a sub study of the RATHL Trial

A prospective study of ovarian function, loss and fertility in young women with Hodgkin Lymphoma

Short title: RATHL Ovarian Sub Study

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Signature	
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Section 1.0: Study Contacts

Lead Investigator for the RATHL Ovarian Sub Study:
Professor Richard Anderson
MRC Centre for Reproductive Health
Queen's Medical Research Institute
The University of Edinburgh
47 Little France Crescent
Edinburgh EH16 4TJ
Tel: 0131 242 6386/2669
Fax: 0131 242 6441
Email: richard.anderson@ed.ac.uk

Chief Investigator of main study (RATHL Trial)
Professor Peter Johnson
Cancer Research UK Clinical Centre
Somers Cancer Research Building
Southampton General Hospital
Southampton
SO16 6YD
Tel: 02380 796186
Fax: 02380 795152
Email: johnsonp@soton.ac.uk

Trial Coordinator:
Mrs Lindsey Stevens
Haematology Trials Group
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ
Tel: 020 7679 9868
Fax: 020 7679 9861
Email: rathl@ctc.ucl.ac.uk

Data Management:
Mr Thomas Roberts
Haematology Trials Group
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ
Tel: 020 7679 9112
Fax: 020 7679 9526
Email: rathl@ctc.ucl.ac.uk

Section 2.0: Introduction

Major advances in therapy over recent years have led to improvements in long-term survival of patients with lymphoma, currently 80%, with up to 95% cure of early stage disease. These developments have led to greater emphasis on the quality of life of cancer survivors and long-term effects of both the disease and its treatment. Prominent among these are adverse effects on fertility. This is particularly prominent in lymphoma where so many of those affected are young: the ability to have a family after cancer treatment is very highly valued by patients[1].

The ovary is sensitive to damage from chemotherapy and radiotherapy, both treatments resulting in the irreversible loss of follicles, the structures which contain the eggs. Initial alkylating agent-based chemotherapy regimens for lymphoma (MOPP, ChlVPP) were a major advance in treatment but were very gonadotoxic, with a high risk of infertility and premature ovarian failure in women. MOPP has now been superceded by ABVD, which is much less gonadotoxic and is the current treatment of choice for most patients, although it is not curative in all. The RATHL trial is a prospective international chemotherapy trial in Hodgkin lymphoma in which patients who are identified to be at increased risk of treatment failure are switched to escalated BEACOPP, an alkylating agent based salvage regime in an attempt to increase cure rates but which is much more gonadotoxic[2]. This trial provides an opportunity to assess acute ovarian toxicity and its relationship with long-term fertility in women receiving ABVD alone or with escalated BEACOPP.

Anti-Mullerian hormone (AMH) is produced by the granulosa cells of small ovarian follicles. AMH is produced as soon as the follicle starts to grow (ie it is not produced by resting, primordial follicles) but expression ceases at the early antral stage. Importantly, this means that serum concentrations do not reflect the dominant follicle in a menstrual cycle, but rather the number of small follicles, sometimes referred to as the ovarian reserve, which in turn is believed to reflect the number of primordial follicles whose depletion signals the menopause. Serum measurement of AMH is becoming established as a valuable measure of the ovarian reserve[3]. AMH declines with age, and a rapid fall has been demonstrated in women receiving chemotherapy for breast cancer and lymphoma[4,5]. Reduced AMH concentrations have been demonstrated in female survivors of childhood cancer[6] and of haematological malignancies[7]. Women treated for HL during childhood who had received MOPP had lower AMH than controls and women treated without alkylating agents[8]. The value of AMH in linking pre-treatment assessment of the ovarian reserve, acute ovarian toxicity and long-term fertility is however unknown as no prospective long-term studies have been performed and it is this that will be assessed in this RATHL Ovarian sub study.

In addition we will offer storage of ovarian tissue in order to define prospectively the uptake of this technique for women of reproductive age facing sterilising chemotherapy, ie those to receive the BEACOPP regimen. This will however be organised separately from the Ovarian substudy.

2.1 Rationale of the Study

This study will collect blood samples from premenopausal women recruited into the RATHL trial and these blood samples will be analysed locally (for LH, FSH, oestradiol) and in Edinburgh (for AMH). Patients will also be asked a number of questions relating to their reproductive and menstrual history.

Premenopausal women aged 35 or less that are PET positive after 2 cycles of ABVD and are scheduled to receive BEACOPP within the RATHL trial will also be offered ovarian cryopreservation in a separate protocol (see section 3.3).

2.2 Study Objective

There are two elements to this sub study:-

1. A prospective analysis of ovarian function during and following chemotherapy for Hodgkin's lymphoma, comparing ABVD with BEACOPP chemotherapy regimens;

2. An observational cohort study of women considering and taking up ovarian cryopreservation for fertility preservation.

Section 3.0: Study Details

3.1 Eligibility Criteria

Site

1. Sites should be able to undertake the additional sampling requirements in the sub study protocol.
2. Sites will need to identify a primary contact for the RATHL Ovarian sub study.

Patient

1. All premenopausal women recruited into the main RATHL trial will be eligible for the sub study.
2. Premenopausal women who consent to take part in the ovarian sub study.

3.2 Study Outline

1. Premenopausal women in the RATHL trial will be approached and this sub study will be discussed with them. They will be provided with a patient information sheet to take away and read.

2. If they agree to participate in the sub study they will be asked to sign a consent form for the RATHL Ovarian sub study.

3. Once they have given their consent patients will have blood taken according to the schedule in Appendix 1 and will be asked a number of questions relating to their reproductive and menstrual history (Appendix 2). Blood samples can be collected at any stage of the menstrual cycle.

4. One blood sample should be taken for measurement of LH, FSH and Oestradiol by the routine hospital biochemistry lab as per normal clinical practice. These results should be recorded on the bottom of the questionnaire (Appendix 2).

5. A second blood sample (7-10ml, serum tube, Appendix 1) should be posted the same day in the prepaid packaging to:

   Anne Saunderson
   Research Nurse
   Clinical Research Room G7238
   Simpson Centre for Reproductive Health
   Royal Infirmary of Edinburgh
   51 Little France Crescent
   Edinburgh EH16 4SA

   Please ensure samples are labelled before posting (labels will be sent out to sites).

6. Questionnaire should be sent to:-

   Ovarian Sub Study Data Manager
   RATHL Team
   Haematology Trials Group
   CR UK & UCL Cancer Trials Centre
   90 Tottenham Court Road
   London W1T 4TJ

   Please ensure that any patient names are blanked out and the questionnaires are marked only with the patients' initials and trial number.

3.3 Ovarian Cryopreservation for Fertility Preservation

It is highly recommended that ovarian cryopreservation is discussed with women who are PET positive after 2 cycles of ABVD and who are scheduled to receive BEACOPP. This option, for women without previous children and under the age of 35, is made available in a separate protocol by the Centre for Reproductive Health in

Edinburgh. It is sponsored by NHS Lothian University Hospital Division and has been approved by Lothian NHS Board and Research Ethics committee.

Patients who consent to go into this study:

1. Would be required to travel to Edinburgh and have a laparoscopy. Their ovarian tissue would then be stored in the fully accredited NHS Tissue Bank in Edinburgh.
2. For further information about how to refer your patient please contact Professor Richard Anderson on 0131 2426386/2422669 or email Richard.Anderson@ed.ac.uk.

Section 4.0 Outcomes

1. Analysis of acute ovarian toxicity by treatment regimen
2. Analysis of post-treatment ovarian function, including progression to ovarian failure, recovery of ovarian function.
3. Subsequent fertility related to pre-treatment ovarian assessment, degree of acute toxicity, post-treatment ovarian function.

Section 5.0 Sample Size

The RATHL Study will recruit approximately 800 patients in the UK. Half will be female and half under 35 years old, thus 200 women will be potentially eligible.

We anticipate high recruitment to the ovarian function substudy, as this is non-invasive only requiring blood sampling which will be performed when samples are taken for routine care and data from an interview.

Approximately 25% of the 200 eligible women (n=50) will have a positive PET scan and potentially be offered ovarian cryopreservation.

Section 6.0 Analysis

The data from this study will be held at the Haematology Trials Group at the CR UK & UCL Cancer Trials Centre and matched with the clinical data from the main study. All analyses will be carried in collaboration with the Centre for Reproductive Biology, Edinburgh.

Primary analyses will include:

- Biochemical and menstrual changes (reflecting ovarian function) during and after chemotherapy, and comparison of treatment regimens
- Analysis of ovarian toxicity in relation to pre-treatment ovarian function
- Analysis of post-treatment fertility in relation to pre-treatment ovarian function, post-treatment ovarian function by patient desire for pregnancy
- Menstrual function and contraceptive use post-treatment

Section 7.0: References

1. Schover LR, et al. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer* 1999; **86**(4)**:** 697-709.
2. Behringer K, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2005; **23**(30)**:** 7555-64.
3. van Rooij IAJ, et al. Serum antimüllerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. *Fertil Steril* 2005; **83**(4)**:** 979-87.
4. Anderson RA, et al. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Human Reprod* 2006; **21**(10)**:** 2583-92.
5. Rosendahl M, et al. Ovarian function after removal of an entire ovary for cryopreservation of pieces of cortex prior to gonadotoxic treatment: a follow-up study. *Hum Reprod* 2008.
6. Bath LE, et al. Depletion of ovarian reserve in young women after treatment for cancer in childhood: detection by anti-Mullerian hormone, inhibin B and ovarian ultrasound. *Hum Reprod* 2003; **18**(11)**:** 2368-74.
7. Lie Fong S, et al. Anti-mullerian hormone as a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies. *Hum Reprod* 2008; **23**(3)**:** 674-8.
8. van Beek RD, et al. Anti-Mullerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood. *J Clin Endocrinol Metab* 2007; **92**(10)**:** 3869-74.

Appendix 1

Sample collection schedule

	Pre-treatment screening/staging (-4 to 0 weeks)	After 2 cycles of ABVD chemotherapy	At the end of all treatment	12 months after the end of all treatment	24 months after the end of all treatment	36 months after the end of all treatment	60 months after the end of all treatment
Interview*	X	X	X	X	X	X	X
AMH**	X	X	X	X	X	X	X
LH, FSH & Oestradiol**	X	X	X	X	X	X	X

*See questionnaires in Appendix 2.

** AMH analysis to be performed in Edinburgh. LH, FSH and Oestradiol to be measured in local hospital lab.

Blood tubes to be used:

Vacutainer system: use gold red, or orange topped blood tubes

Sarstedt system: use white or brown blood tubes

It is important that these are 'serum' tubes, not with additives such as EDTA as these interfere with the assay.

Sample timing: After 2 cycles ABVD

- Please take the blood sample when the patient comes to clinic to get their PET scan result.

Sample timing: At the end of all treatment

- ABVD/AVD groups: the sample should be taken at the first end of treatment follow-up appointment, usually at 1 month post treatment.
- PET 3 Scan (Negative score 1-3): After BEACOPP-14 x 2 or BEACOPP-Escalated x 1: the sample should be taken at the first end of treatment follow up appointment.
- PET 3 Scan (Positive score 4-5): Further chemotherapy: the sample should be taken at the end of all chemotherapy treatment. In primary refractory patients who start salvage after PET scan 3, the sample should be taken at the end of salvage, rather than the end of BEACOPP.

Appendix 2 – Questionnaires: Pre Treatment and Follow Up

Ovarian Sub Study
(RATHL Trial)
Pre-treatment Questionnaire

Date questionnaire completed	dd	mm	yyyy
Questionnaire completed by			
Centre:	Patient Trial No.:		
Initials:			

Please complete the questionnaire in clinic **before** the patient has their first course of ABVD.

Please send completed questionnaire to:
RATHL Ovarian Sub Study Data Manager
Haematology Trials Group
CRUK & UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ

Pre-treatment Questions			
Please complete as appropriate			
Are your periods regular/irregular?* *Regular is cycle length 24-35 days	Regular	Irregular	
When was your last period?	dd	mm	yyyy

Are you using hormonal contraception?	Yes	No
If so, please specify (Combined oral contraceptive pill, Progestogen only pill, Depo Provera, Implanon, Mirena IUS)		
Have you been pregnant in the past?	Yes	No
If yes, when was your last pregnancy (please give year)?	yyyy	
How many times have you been pregnant?		
Have you had any surgery on your ovaries in the past?	Yes	No
If yes, please give details.		

Gonadal Function

Date of test		dd/mm/yyyy
	Value	Units
LH		
FSH		
Oestradiol		

Blood sample for AMH

Has a blood sample been sent to Edinburgh?	Yes	No	
Date of sample	dd	mm	yyyy

Ovarian Sub Study
(RATHL Study)
Follow up Questionnaire

Date questionnaire completed	dd	mm	yyyy
Stage of treatment or followup			
Questionnaire completed by			
Centre:	Patient Trial No:		
Initials:			

Please complete the questionnaire in clinic at the following time points:-

End of 2 cycles of ABVD ☐

End of all treatment ☐

12 months after the end of all treatment ☐

24 months after the end of all treatment ☐

36 months after the end of all treatment ☐

60 months after the end of all treatment ☐

(please indicate which visit this is by ticking the relevant box above)

Please send completed questionnaire to:
RATHL Ovarian Sub Study Data Manager
Haematology Trials Group
CRUK & UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ

Follow up Questions

Please complete as appropriate

Have you continued to have periods during/following treatment since last assessment?	Yes		No
When was your last period?	dd	mm	yyyy

Are you using hormonal contraception?	Yes	No
If so, please specify (COCP, Progestogen only pill, Depo Provera, Implanon, Mirena IUS)		
Have you been pregnant since your treatment?	Yes	No
What was the outcome (Still pregnant, live birth, miscarriage, termination)?		
When do you think you fell pregnant (month/year)?	mm	yyyy
If more than 1 pregnancy since last visit: What was the outcome (Still pregnant, live birth, miscarriage, termination)?		
When do you think you fell pregnant (month/year)?	mm	yyyy
Are you trying to get pregnant at the moment?	Yes	No

Gonadal Function

Date of test		dd/mm/yyyy
	Value	Units
LH		
FSH		
Oestradiol		

Blood sample for AMH

Has a blood sample been sent to Edinburgh?	Yes		No
Date of sample	dd	mm	yyyy