

*The following is a suggested guideline and does not replace ongoing clinical assessment and professional judgment.*

**PURPOSE AND INTENT**

To guide the effective and safe use of Methotrexate as a pharmaceutical agent for the medical management of an ectopic pregnancy and pregnancy of unknown location.

For the purpose of this document, ectopic pregnancy and pregnancy of unknown location will be referred to as ectopic pregnancy.

**1. BACKGROUND**

Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy. Currently, a high index of suspicion, serial hormone assays, and transvaginal ultrasonography facilitate the diagnosis and treatment of ectopic pregnancy before rupture occurs. Early nonsurgical diagnosis and timely treatment have resulted in a dramatic decline in mortality due to ectopic pregnancy. (15). Evidence indicates Methotrexate is an effective and safe pharmaceutical agent for the medical management of an ectopic pregnancy. Methotrexate is a folic acid antagonist preventing DNA replication. It inhibits the rapidly dividing trophoblast cells of an ectopic pregnancy. (2)

**2. DEFINITIONS**

**Definite Ectopic Pregnancy:** extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)

**Probable Ectopic Pregnancy:** inhomogeneous adnexal mass or extrauterine sac-like structure

**Pregnancy of Unknown Location:** no signs of either ectopic pregnancy or intrauterine pregnancy

**Persistent Pregnancy of Unknown Location:** the serum hCG levels fail to decline, there is no evidence of trophoblastic disease and the location of pregnancy cannot be identified using transvaginal ultrasound or laparoscopy

**Probable intrauterine pregnancy:** intrauterine echogenic sac-like structure

**Definite intrauterine pregnancy:** intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity). Barnhart. Nomenclature for pregnancy of unknown location. Fertil Steril 2011.

**3. GUIDELINES**

**3.1 Indications:**

- 3.1.1 A good candidate for methotrexate has the following characteristics:
- hemodynamic stability
  - no active bleeding
  - low serum  $\beta$ -hCG, ideally less than 1500 international Units/Litre but can be up to 5000 international Units/Litre
  - no fetal cardiac activity seen on ultrasound scan
  - certainty that there is no intrauterine pregnancy
  - willingness to attend for follow-up

- no known sensitivity to methotrexate
  - no significant pain
  - normal liver and renal function test
  - an unruptured ectopic pregnancy with a mass smaller than 35 mm with no visible heartbeat  
RCOG Green-top Guideline No. 21 e34 of e55<sup>a</sup> 2016 Royal College of Obstetricians and Gynaecologists
- 3.1.2 Non-tubal ectopic: cervical, cornual, ovarian, and abdominal
- 3.1.3 Persistent ectopic pregnancy following salpingostomy
- 3.1.4 Failed expectant management of ectopic pregnancy or pregnancy of unknown location
- 3.1.5 Pregnancy of unknown location on ultrasound where patient requests termination

### 3.2 Contraindications to Methotrexate Therapy

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> <li>○ Intrauterine pregnancy in a wanted pregnancy</li> <li>○ History of Immunodeficiency Syndrome or Disorders</li> <li>○ Moderate to severe anemia, leukopenia, or thrombocytopenia</li> <li>○ Sensitivity to Methotrexate</li> <li>○ Active pulmonary disease</li> <li>○ Active peptic ulcer disease</li> <li>○ Clinically important hepatic dysfunction</li> <li>○ Clinically important renal dysfunction</li> <li>○ Breastfeeding</li> <li>○ Ruptured ectopic pregnancy</li> <li>○ Hemodynamically unstable patient</li> </ul>	<ul style="list-style-type: none"> <li>○ Embryonic cardiac activity detected by transvaginal ultrasonography</li> <li>○ High initial <math>\beta</math>-hCG concentration (&gt;5,000 IU/mL)</li> <li>○ Ectopic pregnancy greater than 40 mm in size as imaged by transvaginal ultrasonography</li> <li>○ Refusal to accept blood transfusion</li> <li>○ Inability to participate in follow-up</li> </ul>

Adapted Practice Committee. Medical treatment of ectopic pregnancy. Fertil Steril 2013.

### 3.3 Treatment and drug side effects associated with Methotrexate

- 3.3.1 Treatment side effects:
- Increase in abdominal girth
  - Increase in  $\beta$ -hCG during initial therapy
  - Vaginal bleeding or spotting
  - Abdominal pain
- 3.3.2 Drug side effects
- Gastric distress, nausea, and vomiting
  - Stomatitis
  - Dizziness
  - Severe neutropenia (rare)
  - Reversible alopecia (rare)
  - Pneumonitis (rare)

Practice Committee. Medical treatment of ectopic pregnancy. Fertil Steril 2013.

Rupture is possible even several weeks after Methotrexate treatment.  
Expect some abdominal pain for two to four days after Methotrexate treatment.

If severe pain is experienced:

- clinically reassess
- complete serial hemoglobins
- repeat ultrasound
- consider surgery

**3.4 Pre-Treatment Lab Results**

- 3.4.1 CBC
- 3.4.2 Liver enzymes (AST, ALT, GGT, LDH, Alkaline phosphate), and creatinine
- 3.4.3 Quantitative  $\beta$ -hCG (day 1)
- 3.4.4 RH status
  - Unknown – determine
  - RH negative – treat Rho (D) Immune Globulin (WinRho SDF™)  
Best Blood Manitoba GUIDELINES FOR PERINATAL TESTING and ADMINISTRATION OF WINRHO® SDF (Rh IMMUNE GLOBULIN)

**3.5 Methotrexate administration**

- 3.5.1 Methotrexate is a cytotoxic medication. Follow WRHA policy [110.160.010 Safe Handling of Hazardous Medication \(Cytotoxic and Non-Cytotoxic\)](#) during preparation, administration, and disposal of this medication.
- 3.5.2 50 mg/m<sup>2</sup> IV or IM. Administration of this drug is height and weight dependent. Please refer to dose banding table. Dosing is rounded to the nearest 5 mg. Dose banding calculation is incorporated into EPR (SBH) and on reverse of order sheet (HSC) (See Appendix A).
- 3.5.3 Discontinue any medications containing folic acid (folate) including prenatal vitamins.
- 3.5.4 Refer to [Methotrexate Drug Monograph](#) in the WRHA/Shared Health Adult Parenteral Drug Monograph for information regarding this medication.
- 3.5.5 Methotrexate is only available from either the Health Sciences Centre or St. Boniface Hospital Pharmacies; all other WRHA sites will need to transfer patients to HSC or SBH.

**3.6 Treatment Protocol - Ectopic Pregnancy**

**SINGLE DOSE PROTOCOL**

- Day 1  $\beta$ -hCG, Methotrexate as above
- Day 4 Repeat  $\beta$ -hCG
- Day 7 Repeat  $\beta$ -hCG. Reassess treatment plan. If there is a 15% decline, continue weekly surveillance. Consider repeating Methotrexate if less than a 15% decline from day 4 to day 7. If repeat Methotrexate treatment is implemented, repeat bloodwork and restart the regimen following the chart on form 'DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy'. (NS00832-HSC, 7102-4300-4-SBH)  
**Note:** There is no benefit in giving a third dose.
- Day 14 Repeat  $\beta$ -hCG, CBC  
Weekly quantitative  $\beta$ -hCG until less than 10 International Units/Litre

**TWO-DOSE PROTOCOL**

CONSIDER USE IF INITIAL BHCG >3600

- Day 1  $\beta$ -hCG, Methotrexate as above
- Day 4 2<sup>ND</sup> DOSE OF Methotrexate,  $\beta$ -hCG
- Day 7 repeat  $\beta$ -hCG, follow protocol as above for SINGLE DOSE
- Day 14 repeat  $\beta$ -hCG, CBC

**NOTE: Resolution time is 14 to 90 days.**

**Practice Guideline:**

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- Rupture is possible even several weeks after Methotrexate treatment**  
**Expect some abdominal pain for two to four days after Methotrexate treatment**  
**If severe pain is experienced, then clinically reassess and do:**
- Serial hemoglobins
  - Repeat ultrasound and consider surgery

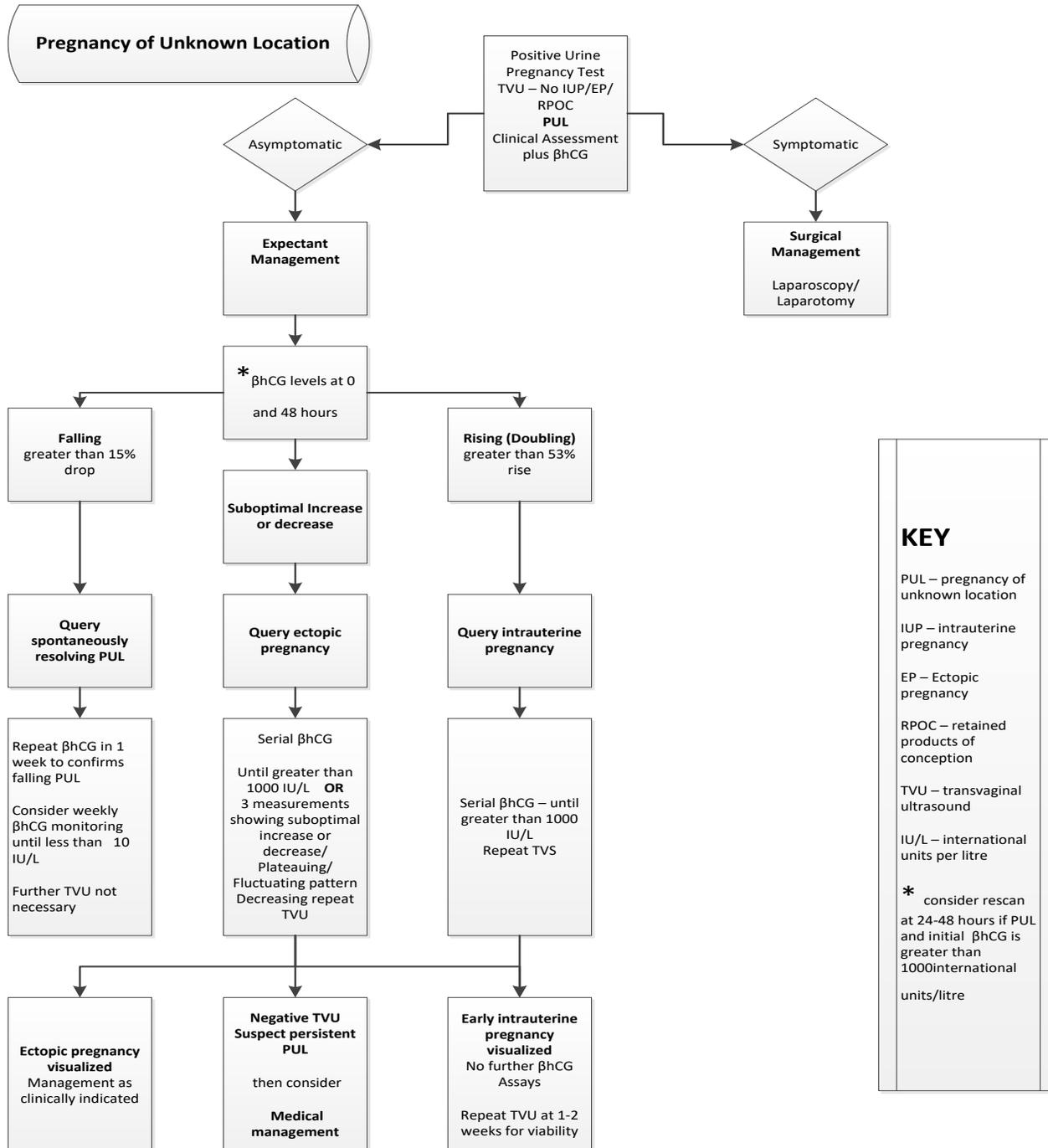
Success of single dose Methotrexate for ectopic pregnancy according to  $\beta$ -hCG concentration

$\beta$ -hCG concentration (IU/L)	Number of women successfully treated (percent)	Number of women failing treatment (percent)
<1000	133 (99)	2 (1)
1000 to 1999	51 (94)	3 (6)
2000 to 4999	106 (96)	4 (4)
5000 to 9999	42 (86)	7 (14)
10,000 to 150,000	18 (82)	4 (18)

Adapted from: Menon, S, et al. Establishing a human chorionic gonadotropin cutoff to guide Methotrexate treatment of ectopic pregnancy: a systematic review. Fertil Steril 2007; 87:481. Graphic 74836 Version 2.0

3.7 Patient education and follow-up information

Utilize the WRHA, Women’s Health Program DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy HSC NS00832, SBH 7102-4300-4



Pregnancy of Unknown location: An evidenced based approach to management. *The Obstetrician & Gynecologist*, 10.15676/toag. 10.4.224.27438. [www.rcog.org.uk/togonline](http://www.rcog.org.uk/togonline)

#### 4. REFERENCES:

- (1) American College of Obstetricians and Gynecologists (ACOG). (2008). Practice bulletin No. 94: medical management of ectopic pregnancy. *Obstetrics & Gynecology*, 111(6), 1479-1485.
- (2) Barnhart, K. T. (2009). Ectopic pregnancy. *New England Journal of Medicine*, 361(4), 379-387.
- (3) Barnhart, K.T., Gosman, G., Ashby, R., & Sammel, M. (2003). The medical management of ectopic pregnancy: A meta-analysis comparing “single dose” and “multidose” regimens. *Obstetrics & Gynecology*, 101(4), 778-784.
- (4) Barnhart, K., van Mello, N. M., Boure, T., Kirk, E., Van Calster, B., Bottomley, C., Chung, K... Timmerman, D. (2011). Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertility and Sterility*, 95(3), 853 – 866.
- (5) Best Blood Manitoba GUIDELINES FOR PERINATAL TESTING and ADMINISTRATION OF WINRHO® SDF (Rh IMMUNE GLOBULIN) (2017) retrieved from <https://blood.ca/en/hospitals/winnipeg-centre/Perinatal-Services>
- (6) Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk EJ, on behalf of the Royal College of Obstetricians and Gynaecologists. (2016) Diagnosis and management of ectopic pregnancy. *BJOG British Journal of Obstetricians and Gynaecologists*
- (7) Lipscomb, G.H., McCord, M.D., Stovall, T.G., Huff, G., Portera, S.G., & Ling, F.W. (2000). Predictors of success of Methotrexate treatment in women with tubal ectopic pregnancies. *New England Journal of Medicine*, 341(26), 1974-1978.
- (8) Lipscomb, G.H., Stovall, T.G., & Ling, F.W. (2000). Nonsurgical treatment of ectopic pregnancy. *New England Journal of Medicine*, 343(18): 1325-1329.
- (9) McQueen, A. (2011). Ectopic pregnancy: Risk factors, diagnostic procedures and treatment. *Nursing Standard*, 25(37), 49-56.
- (10) Menon S, Colins J, Barnhart KT. et al. (2007). Establishing a human chorionic gonadotropin cutoff to guide Methotrexate treatment of ectopic pregnancy: a systematic review. *Fertility and Sterility* 87:481.
- (11) Mosby’s Nursing Skills, Patient Education Content. ‘Ectopic Pregnancy: Treatment with Methotrexate’ (Document re-released 01/09/2011). Retrieved from:  
<http://mns.elsevierperformancemanager.com/NursingSkills/PatientEducation.aspx?DocID=10087&UrlID=42444&SID=47660>
- (12) Sagali, H, & Mohamed, K. (2008) Pregnancy of Unknown location: An evidenced based approach to management. *The Obstetrician & Gynecologist*, retrieved from. [www.rcog.org.uk/togonline](http://www.rcog.org.uk/togonline)
- (13) Tang, A., Baartz, D., & Khoo, S. (2006). A medical management of interstitial ectopic pregnancy: A 5-year clinical study. *Australian & New Zealand Journal of Obstetrics & Gynaecology*, 46(2), 107-111.
- (14) Tenore, J. L. (2000). Medical treatment of ectopic pregnancy: a committee opinion 11: Ectopic pregnancy. *American Family Physician*, 61(4), 1080-1088.
- (15) The Practice Committee of the American Society for Reproductive Medicine. (2013). Medical treatment of ectopic pregnancy: a committee opinion. *Fertility and Sterility*®, 100(3), 638 – 644.
- (16) American College of Obstetricians and Gynecologists (2018). Practice Bulletin No.191. Tubal Ectopic Pregnancy. *Obstetrics & Gynecology*, 131(2)e65-e77

#### 6. PRIMARY AUTHOR (S)

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**CLINICAL PRACTICE GUIDELINE**

**Practice Guideline:**

*Medical and Expectant Management of Ectopic Pregnancy and Pregnancy of Unknown Location*

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**Appendix A**

**Women's Health Program  
Methotrexate for Treatment  
of Ectopic Pregnancy**

DATE  
PATIENT  
DOB  
HSC NO.

*These orders are to be used as a guideline and do not replace sound clinical judgment and professional practice standards. Patient allergy and contraindications must be considered when completing these orders.*  
 Standard orders. If not in agreement with an order, cross out and initial.  Requires a check (✓) for activation.

Drug Allergies ▶

ORDER TRANSCRIBED AND ACTIVATED

**R**

**MEDICATION ORDERS**  
TO BE INITIATED OR DISCONTINUED

PAGE 1 OF 1

TEST DONE

DATE

TIME

Height \_\_\_\_\_ cm Weight \_\_\_\_\_ kg

Methotrexate \_\_\_\_\_ mg IM x 1 dose  
(dose 50 mg/m<sup>2</sup> rounded to the nearest 5 mg as defined in the table on the reverse page)

If the patient height and weight cannot be found in the table on the reverse page, physician may manually calculate the Body Surface Area (BSA)

BSA = \_\_\_\_\_

PHYSICIAN'S SIGNATURE \_\_\_\_\_ MD

TRANSCRIBED: \_\_\_\_\_ REVIEWER: \_\_\_\_\_

PRINTED NAME \_\_\_\_\_ MD  
GENERIC EQUIVALENT AUTHORIZED

FAXED DATE: \_\_\_\_\_ TIME: \_\_\_\_\_ INITIALS: \_\_\_\_\_

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		Methotrexate DOSE of 50 mg/m <sup>2</sup> rounded to nearest 5 mg														
Height (cm)	Min	60 mg	65 mg	70 mg	75 mg	80 mg	85 mg	90 mg	95 mg	100 mg	105 mg	110 mg	115 mg	120 mg	125 mg	130 mg
Max		Find patient's height in rows at left, then read across and find weight (kg) in correct column below. Dose is read above.														
126	127.9	38-44	45-51	52-59	60-68	69-77	78-87	88-97	98-108	109-119	120-130					
128	129.9	37-43	44-50	51-58	59-67	68-76	77-85	86-95	96-106	107-117	118-128					
130	131.9	37-42	43-50	51-57	58-66	67-74	75-84	85-94	95-104	105-115	116-127	128-138				
132	133.9	37-42	43-49	50-56	57-65	66-73	74-82	83-92	93-103	104-114	115-125	126-136				
134	135.9	36-41	42-48	49-56	57-64	65-72	73-81	82-91	92-101	102-112	113-123	124-134				
136	137.9	35-41	42-48	49-55	56-63	64-71	72-80	81-90	91-100	101-110	111-121	122-132				
138	139.9	35-40	41-47	48-54	55-62	63-70	71-79	80-88	89-98	99-109	110-120	121-130				
140	141.9	34-40	41-46	47-53	54-61	62-69	70-78	79-87	88-97	98-107	108-118	119-128				
142	143.9	34-39	40-46	47-53	54-60	61-68	69-77	78-86	87-95	96-106	107-116	117-127	128-138			
144	145.9	33-38.9	39-45	46-52	53-59	60-67	68-76	77-85	86-94	95-104	105-115	116-126	127-136			
146	147.9	33-38	39-44	45-51	52-58	59-66	67-75	76-83	84-93	94-103	104-113	114-124	125-134			
148	149.9	32-37	38-44	45-50	51-58	59-65	66-74	75-82	83-91	92-101	102-111	112-122	123-133			
150	151.9	32-37	38-43	44-50	51-57	58-64	65-73	74-81	82-90	91-100	101-110	111-121	122-131			
152	153.9	31.5-36.9	37-43	44-49	50-56	57-64	65-72	73-80	81-89	90-99	100-109	110-119	120-129			
154	155.9	31-36	37-42	43-49	50-55	56-63	64-71	72-79	80-88	89-97	98-107	108-117	118-128	129-138		
156	157.9	30.5-35.9	36-41	42-48	49-55	56-62	63-70	71-78	79-87	88-96	97-106	107-116	117-127	128-137		
158	159.9		35.5-41	42-47	48-54	55-61	62-69	70-77	78-86	87-95	96-104	105-114	115-125	126-136	137-146	
160	161.9		35.5-40.9	41-47	48-53	54-61	62-68	69-76	77-85	86-94	95-103	104-113	114-123	124-134	135-145	
162	163.9		35-40	41-46	47-53	54-60	61-67	68-75	76-84	85-93	94-102	103-112	113-122	123-132	133-144	
164	165.9		34.5-39.9	40-45	46-52	53-59	60-66	67-74	75-83	84-91	92-101	102-110	111-120	121-131	132-142	
166	167.9		34-39	40-45	46-52	53-58	59-66	67-74	75-82	83-90	91-99	100-109	110-119	120-129	130-140	141-151
168	169.9		33.5-38.9	39-44.9	45-51	52-58	59-65	66-73	74-81	82-89	90-98	99-108	109-117	118-128	129-138	139-149
170	171.9		33-38	39-44	45-50	51-57	58-64	65-72	73-80	81-88	89-97	98-106	107-116	117-126	127-137	138-148
172	173.9			38-43.9	44-50	51-56	57-63	64-71	72-79	80-87	88-96	97-105	106-115	116-125	126-135	136-146
174	175.9			38-43	44-49	50-56	57-63	64-70	71-78	79-86	87-95	96-104	105-113	114-123	124-134	135-144
176	177.9			37.5-42.9	43-48.9	49-55	56-62	63-69	70-77	78-85	86-94	95-103	104-112	113-122	123-132	133-143
178	179.9			42.5-48	49-54.9	55-61	62-69	70-76	77-84	85-93	94-102	103-111	112-120	121-131	132-141	133-141
180	181.9			42-47.9	48-54	55-61	62-68	69-75	76-83	84-92	93-100	101-110	111-119	120-129	130-139	130-139
182	183.9			42-47	48-53	54-60	61-67	68-75	76-82	83-91	92-99	100-108	109-118	119-128	129-138	129-138
184	185.9			42-46.9	47-53	54-59	60-66	67-74	75-82	83-90	91-98	99-107	108-117	118-126	127-137	127-137
186	187.9			46.5-52	53-59	60-66	67-73	74-81	82-89	90-97	98-106	107-115	116-125	126-135	126-135	126-135
188	189.9			46-52	53-58	59-65	66-72	73-80	81-88	89-96	97-105	106-114	115-124	125-134	125-134	125-134
190	191.9			45.5-51	52-57.9	58-64	65-71	72-79	80-87	88-95	96-104	105-113	114-122	123-132	123-132	123-132
192	193.9			45-50.9	51-57	58-64	65-71	72-78	79-86	87-94	95-103	104-112	113-121	122-131	122-131	122-131

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**Appendix B**

**Women’s Health Program**

Date: \_\_\_\_\_

Number of pages faxed: \_\_\_\_\_

Fax to: Dr \_\_\_\_\_

Fax Number: \_\_\_\_\_

**Fax from:**

Women’s Health Ambulatory Care  
Health Sciences Centre  
WR035 – 735 Notre Dame Avenue  
FAX number: 204-787-2876

Antepartum Gynecology Inpatient Unit  
Health Sciences Centre  
WRS5 – 735 Notre Dame Avenue  
FAX number: 204-787-2875

Antepartum Gynecology Inpatient Unit  
St Boniface Hospital  
409 Tache Ave.  
FAX number: 204-237-2294

St. Boniface Emergency Department  
St Boniface Hospital  
409 Tache Ave.  
FAX number: 204-237-2268

Dear Dr \_\_\_\_\_:

You have received this fax because you have been identified as the responsible physician ordering methotrexate for the patient identified on the attached form. Please arrange for follow-up including scheduling and reviewing  $\beta$ -hCG tests, on your patient.

Please see the attached form: Women’s Health Program DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy.