Gold Therapy in Women Planning Pregnancy: Outcomes in One Center

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ABSTRACT. ***Objective.*** To review the experience and outcome of pregnancies in women taking gold while planning pregnancy.

Methods. We undertook a chart review of patients attending for gold injection and monitoring between January 1992 and April 2006. For women who became pregnant while being followed taking gold therapy, we extracted demographic, treatment, and disease activity data, information regarding pregnancy complications, outcome, and postpartum course. For details missing from the clinic records, patients were interviewed by the clinic nurse.

Results. Fourteen women experienced 20 pregnancies while being followed in the gold monitoring clinic. Mean age at the time of conception was 34.5 years (range 24–41), disease duration 8.5 years (1–16). Rheumatoid factor was positive in 9 of 14 women. Duration taking gold prior to conception was < 12 months in 7 pregnancies, 13–24 months in 4, 25–34 months in 2, and 2–10 years in 7 pregnancies. Four women continued taking gold until delivery. The rest of the women discontinued gold when they knew they were pregnant, with the exception of one who held her gold 4 weeks prior to conception. There were 5 spontaneous abortions in the first trimester; included were 2 spontaneous abortions in a woman with known Robertsonian chromosomal translocation. Sixteen babies were healthy including a pair of twins. One baby was born with weakness of one extraocular muscle requiring surgery; one had blocked tear ducts at birth. Rheumatoid arthritis (RA) flared during 3/15 completed pregnancies and postpartum and post-spontaneous abortion in 18/20 pregnancies.

Conclusion. Our clinic experience and the published literature support the current practice that in patients with RA, gold may still be considered a treatment option in women planning pregnancy. (First Release August 1 2007; J Rheumatol 2007;34:1827–31)

Key Indexing Terms:
GOLD RHEUMATOID ARTHRITIS PREGNANCY MYOCHRYSINE
SOLGANAL DISEASE MODIFYING ANTIRHEUMATIC DRUGS

The amelioration of signs and symptoms of rheumatoid arthritis (RA) during pregnancy is well documented in the published literature, occurring in 56%–86%[1-4]. A postpartum flare occurring typically between 1 and 16 weeks can be anticipated.

In women planning pregnancy, the most commonly used disease modifying antirheumatic drugs (DMARD) for RA must be discontinued due to risk of teratogenicity. This is the case for methotrexate (MTX) and for leflunomide. The safety of anti-tumor necrosis factor (TNF) and other biological agents used at conception and in women who are pregnant is being evaluated in postmarketing studies.

At the Mary Pack Arthritis Centre, a drug monitoring program for injectable gold has operated for 40 years. Between 30 and 50 new patients are referred annually for medication administration, drug monitoring, and self-injection education. In 2007 there are 270 patients being managed in the clinic; more than half of these patients are monitored for DMARD combinations with gold.

We have reviewed the clinic charts dating from 1992 to identify all women who were followed in the gold clinic while planning pregnancy and who did become pregnant while being followed in our drug monitoring program.

MATERIALS AND METHODS

Records of all patients seen in the gold clinic between January 1992 and January 2006 were reviewed to identify women planning pregnancy. Patients were included if they reported to the nurse or physician that they intended to become pregnant and then did become pregnant during the followup, or if they reported that they were pregnant at any time during the study period while being followed in the gold clinic. Each patient was contacted by the study nurse for telephone interview to confirm and complete the data collection.

The gold product prescribed was gold sodium aurothiomalate, with the exception of one patient who was using gold sodium aurothioglucose at the time of conception. No testing of antiphospholipid antibodies is routinely done.

The following data were collected for each pregnancy: age, disease duration, rheumatoid factor (RF), duration taking gold therapy, mean dose of gold, time to conception, time from conception to gold discontinuation due to pregnancy, pregnancy complications and peripartum complications and pregnancy outcome, DMARD use other than gold, time to postpartum flare, and time until women resumed gold postpartum. In those women with pregnancies prior to gold treatment, details regarding pregnancy complications and preg-

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nancy outcome were collected for those pregnancies prior to gold therapy and prior to onset of RA. RA disease activity was designated as controlled or flared based on information in clinic record and nurse-administered questions. RA was considered controlled if this was the assessment of the clinic rheumatologist, if there were fewer than 4 swollen or tender joints, and if no new prescription of prednisone or nonsteroidal antiinflammatory drugs was required.

As the number of patients and pregnancies prior to gold and while being followed in the gold clinic are small, the results are presented as descriptive and no statistical analysis has been applied to the data.

RESULTS

Between 1992 and 2006, 14 women experienced 20 pregnancies while being followed in the gold monitoring clinic. Patient and disease characteristics, pregnancy numbers during and prior to gold treatment, and duration of gold at conception are included in Table 1. Mean age at time of pregnancy was 34.5 years (range 24–41) and disease duration 8.5 years (1–16). RF was positive in 9 of 14 women. Duration taking gold prior to conception was less than 12 months in 7 pregnancies, 13–24 months in 4 pregnancies, 25–34 months in 2 pregnancies, and 2–8 years in 7 pregnancies. Six patients with RA in our clinic cohort had experienced a total of 11 pregnancies prior to gold therapy. Ten patients had never had MTX prior to conception. Four had discontinued MTX 8–16 months prior to conception.

Information regarding gold dose and other DMARD use at conception, time to conception and duration taking DMARD after conception is included in Table 2. The mean dose of gold while planning pregnancy and prior to conception was 25–50 mg/wk in 13 pregnancies, 50 mg/2 wks in 2 pregnancies, 60 mg/wk in 1 pregnancy, 5–10 mg/wk in 2 pregnancies, and 10 mg every 2 weeks in 2 pregnancies.

Time to conception was less than 4 months in 8 pregnancies, 5–12 months in 7 pregnancies, 36 months in 1 pregnancy, 60 months in 1 pregnancy; in the case of 3 pregnancies, patients reported that the pregnancy was unplanned.

In 20 pregnancies, there were 5 spontaneous abortions during the first trimester. One of these occurred in a 37-year-old woman (Patient 7) with seropositive RA and a history of recurrent pregnancy loss; her obstetrical history prior to gold therapy included 2 live births and one stillbirth before onset of RA, and 1 spontaneous abortion and 1 ectopic pregnancy after onset of RA while not taking DMARD. Patient 3, with 2 spontaneous abortions while taking gold, has a known Robertsonian translocation (chromosome 13, 14). Patients 4 and 6 each had one healthy baby and one spontaneous abortion while being followed in the gold monitoring clinic.

Gold was continued through pregnancy and postpartum in 4 pregnancies (dose 5–10 mg/wk in 3 pregnancies and 50 mg weekly in 1 pregnancy). Gold was discontinued 1–12 weeks after conception in 10 pregnancies, and discontinued 4 weeks prior to conception in Patient 14. One patient who continued gold throughout pregnancy also continued hydroxychloroquine. Patient 1 started sulfasalazine early in pregnancy after discontinuing gold.

RA disease control in pregnancy, pregnancy complications, outcome, and time to postpartum flare of RA are included for each pregnancy in Table 3. RA flared during 3/15 completed pregnancies, and was controlled in 12/15. Flare of RA was

Table 1. Patient, disease, and treatment characteristics.

Patient	Age	RA Duration, yrs	RF +/–	No. of Pregnancies Prior to Gold	No. of Pregnancies During Gold Therapy	MTX Discontinued Prior to Conception, mo	Duration of Gold Use at Conception, mo
1	24	1	+	1	1	8	8
2	35	6	+	0	1	9	12
3	36	9	–	2	2	NA	2.5
	37	10			2	NA	6
4	35	15	+	0	2	NA	15
	36	16		0	2	NA	25
5	34	15	+	0	1	NA	55
6	36	7	+	0	2	NA	83
	40	11		0	2	NA	123
7	36	3	+	5	1	14	9
8	34	7	–	0	1	NA	72
9	36	5	+	1	2	16	15
	40	9		1	2	NA	63
10	38	6	–	0	2	NA	9
	39	7		0	2	NA	24
11	36	2	–	0	1	NA	23
12	29	3	+	1	1	NA	8
13	21	3	–	0	2	NA	33
	24	6		0	2	NA	69
14	41	13	+	0	1	NA	96

NA: not applicable: these patients had never used methotrexate. RF: rheumatoid factor.

Table 2. RA treatment while planning pregnancy and at conception.

Patient	Age	Year	Time to Conception, mo	Gold Dose at Conception	DMARD at Conception	Time to Discontinuation of Gold Post-conception, wks	Time to Discontinuation of other DMARD Post-conception, wks
1	24	2002	6	50 mg/wk	SS 1500 mg/day	4	Continue SSA
2	35	2004	5	50 mg/2 wks		3	
3	36	1997	36	50 mg/wk	HCQ 400 mg/day	5	6
	37	1998	9	45 mg/wk		NA	
4	35	1992	3	50 mg/wk		NA	
	36	1993	3	50 mg/2 wks		2	
5	34	2003	2	5 mg/wk		NA	
6	36	2000	9	10 mg/2-wks		3	
	40	2003	9	50 mg/wk		5	
7	37	1999	7	35 mg/wk		NA	
8	34	2002	12	10 mg/wk	HCQ 400 mg/day	NA	NA
9	36	2001	< 1	60 mg/wk	HCQ 400 mg/day	2	4
	40	2005	4	50 mg/wk	HCQ 400 mg/day + etanercept	2	Etanercept stopped 2 wks post-conception
10	38	1999	< 1	40 mg/wk	HCQ 400 mg/day	2	7
	39	2000	< 1	50 mg/1 wk	HCQ 400 mg/day	2	2
11	36	2000	1	50 mg/1 wk		1	
12	31	2003	*	10 mg/2 wks		NA	
13	21	2001	*	50 mg/wk		NA	
	24	2003	*	50 mg/wk		12	
14	41	2003	60	30 mg/wk	HCQ 400 mg/day	Stopped 4 wks prior to conception	Stopped 4 wks prior to conception

* Unknown. HCQ: hydroxychloroquine, SSZ: sulfasalazine; DMARD: disease modifying antirheumatic drugs. NA: not applicable, patient continued gold or DMARD throughout pregnancy.

treated with prednisone up to 15 mg and with naproxen. Pregnancy complications included hypertension in 1 pregnancy requiring induction at 36 weeks and hyperemesis and hypertension in 1 pregnancy. Sixteen babies were healthy, mean weight 7 lb 4.7 oz in 14 singletons and twins weighing 4 lb 10 oz and 3 lb 10 oz. One baby was born with cysts blocking his tear ducts and one had weakness of one extraocular muscle, requiring surgical correction.

RA flared 2–20 weeks postpartum in 13/15 completed pregnancies and 2–6 weeks postpartum after 5 spontaneous abortions. Two women did not experience postpartum flare. In 20 pregnancies, gold was continued throughout pregnancy and postpartum in 4, and until the time of spontaneous abortion in 3. Gold was discontinued 1 month prior to conception in 1, and discontinued when the patients learned they were pregnant and resumed 1–24 weeks postpartum in 12 pregnancies.

Six of 14 women who took gold while planning pregnancy had experienced a total of 11 pregnancies prior to gold. Seven of these 11 pregnancies were prior to onset of RA (mean 5 yrs) and 4 were after onset of RA (mean 5 yrs) and before gold therapy. Regarding these pregnancies prior to gold, there were 7 live births, 2 spontaneous abortions, 1 stillbirth at 30 weeks, and 1 ectopic pregnancy. One patient, Patient 7, had experienced 3 out of 4 of these pregnancy losses prior to gold and also experienced one spontaneous abortion while receiving gold. One patient, Patient 9, had experienced one spontaneous abortion prior to gold therapy and had 2 healthy babies while being followed in our gold clinic.

DISCUSSION

There are limited DMARD options for women planning pregnancy. MTX and leflunomide are teratogenic. The effects of anti-TNF agents on conception and on the developing fetus are currently being studied[5,6]. Due to long experience with use of gold in women with RA, there is an accumulation of experience that suggests that gold is safe in women planning pregnancy. Although much of this experience has been published, there is a lack of awareness of this option for women planning pregnancy. A recent review of the topic of antirheumatic drugs in pregnancy included no mention of gold[1].

Tarp and Graudal reported no adverse effects on pregnancy or fetal development in 10 pregnancies when women were taking gold at the time of conception[7]. The number of weeks of gold exposure ranged from 2 to 9 weeks. Outcomes included 2 therapeutic abortions, one stillbirth due to tightly knotted umbilical cord, and 7 healthy live births. Seven years later the children born healthy remained physically and psychologically well. Myamoto, *et al* reported no evidence of teratogenesis in infants of 26 mothers who received gold throughout pregnancy; a further 43 women who discontinued gold early or

Table 3. 20 pregnancies in 14 women — pregnancy complication, outcome, and post postpartum (PP) therapy.

Patient	DMARD During Pregnancy	RA Flare During Pregnancy, Yes/No	Pregnancy, Birth, and Baby Outcome	Baby wt	Time to PP Flare, wks	Gold Resumed PP, wks
1	SSZ	N	Healthy	7 lbs 12 oz	12	18
2	Nil	N	PIH, IUGR, healthy	5 lb	16	24
3	Nil	N	SA at 10 wks, Robertsonian translocation (Chrom some 13, 14)	NA	4	4
	Gold 45 mg/wk	N	SA at 10 wks	NA	4	NA
4	Gold 50 mg/wk	N	SA at 7 wks	NA	3	NA
	Nil	N	Healthy	7 lb 11 oz	8	12
5	Gold 5 mg/wk	N	Blocked tear duct, healthy	7 lb 9 oz	20	NA
6	Nil	N	Healthy	8 lb 8 oz	12	12
	Nil	N	SA at 8 wks	NA	4	4
7	Gold 35 mg/wk	N	SA at 6 wks	NA	6	NA
8	Gold 10 mg/wk HCQ 400 mg/day	N	Healthy	7 lb 7 oz	No flare	NA
9	HCQ	Y	PIH, HG, healthy	6 lb 14 oz	4	4
	HCQ	Y	Healthy	6 lb 2 oz	4	4
10	Nil	N	Healthy, mild Duanes syndrome	7 lb 1 oz	8	8
	Nil	N	Healthy	7 lb 3 oz	4	4
11	Nil	N	Healthy	7 lb 3 oz	No flare	No
12	Gold 10 mg/2 wks	N	Healthy	9 lb 1 oz	4	NA
13	Gold 50 mg/wk	N	Healthy	6 lb 3 oz	3–4	NA
	Nil	N	Twins healthy	M = 4 lb 10 oz F = 3 lb 10 oz	3–4	4
14	Nil	Y	Healthy	NA	4	4

NA: not applicable: patient continued gold with or without DMARD throughout pregnancy. SA: spontaneous abortion; PIH: pregnancy induced hypertension; IUGR: intrauterine growth retardation; PP: post partum; SSZ: sulfasalazine; HCQ: hydroxychloroquine.

mid-pregnancy had healthy babies, although 2 babies had hip "anomalies"[8].

Cohen, *et al* reported no adverse effects on pregnancy or baby in a 21-year-old woman who took 100 mg of gold monthly throughout pregnancy[9]. In this report documented in a letter, patient maternal serum gold was 19.9 µmole/l. Umbilical cord gold was 11.4 µmole/l, demonstrating transplacental passage of gold. Serum gold concentrations measured in the infant decreased over time in a manner corresponding to reduction in gold levels of women discontinuing gold. In this letter, the authors reviewed briefly what had previously been reported regarding experience of mothers taking gold in pregnancy and concluded that "gold therapy in pregnancy can be safely continued in patients whose rheumatoid arthritis is of such severity to warrant it." Rayburn writes in the chapter Connective Tissue Disorders in Pregnancy in the textbook *Drug Therapy in Pregnancy* that, "at this time gold therapy is not contraindicated during pregnancy if necessary for maternal health"[10].

In the normal population, 10% to 15% of clinically recognized pregnancies will result in fetal loss. Chromosomal defect is the most common known cause of fetal loss. Maternal age is an important contributing factor. The clinical pregnancy loss rate in women over age 40 years is double that in women under 20 years. In women age 35–39 the rate of fetal loss is 18.7% and in age 40–44 the expected rate is 33.8%[11,12].

In our small series of women taking gold for RA while planning pregnancy, 5 of 20 pregnancies ended in spontaneous abortion. These women's mean age was 34.5 years. Two of these 5 spontaneous abortions occurred in a woman with a known chromosomal defect. Chromosomal defect is the most common cause of fetal loss in the normal population. In our patients who had been pregnant prior to receiving gold, 4 of 11 pregnancies prior to gold were associated with fetal loss, 3 of these in one woman.

Major congenital anomalies affect 2%–3% of live newborns. This number rises by another 2% at age 5 years[13]. One baby in our series had weakness of one extraocular muscle requiring surgery. One baby was born with blocked tear ducts. Major congenital anomalies were not seen in our series. Our sample is small, but it does not appear that pregnancy loss or outcome is affected by gold therapy taken at the time of conception.

A shortcoming related to our retrospective chart review is that we did not include women who were trying to conceive

and had not conceived during the period of study. Men with RA taking gold were not studied.

The subject of pregnancy complications and outcome in RA has received some attention in the literature. Kay and Bach reported lower rates of pregnancy in subjects with RA compared with age-, education-, and address-matched controls[14]. Van Dunne, *et al* found a correlation between miscarriage prior to RA and severity of RA measured by Sharp score[15]. Nelson, *et al* reported reduced fecundity prior to RA onset in 59 women; reduced fecundity was defined as greater than 12 months time to conception; one explanation included in the discussion was the possibility of early pregnancy loss[16].

We did not measure serum concentrations of gold in mother or in infants. It is known that there is transplacental passage of gold. Further, there is evidence of excretion of gold in breast milk[9,17]. It must be assumed, therefore, that there may be risks of typical gold side effects in exposed infants if gold is continued in pregnancy and in lactating mothers. These risks are discussed with the parents if a decision is made to continue gold in these circumstances. The American Academy of Pediatrics classifies gold treatment as compatible with breastfeeding[18].

Our experience adds to the literature to date that indicates that gold may still be considered a treatment option in women planning pregnancy.

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