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Il Carcinoma della Tiroide in Gravidanza

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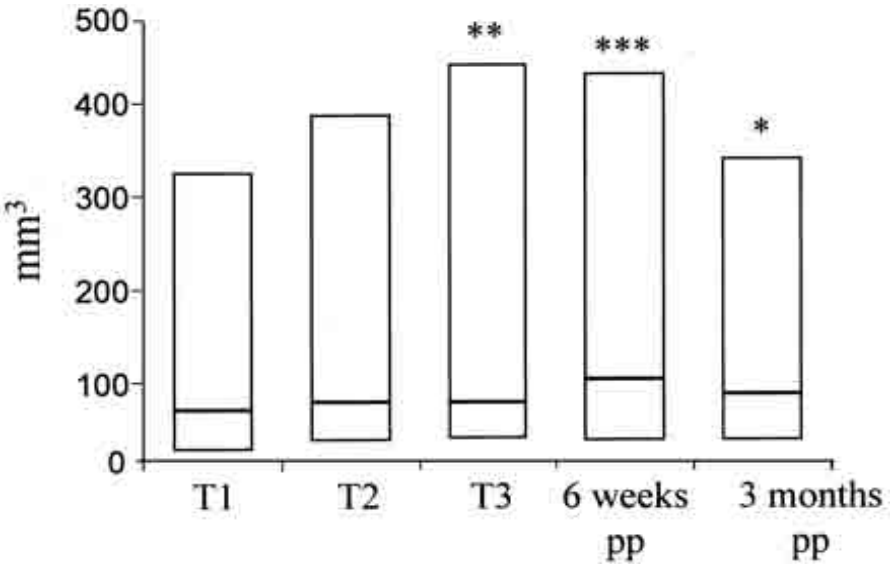
Questions for Clinical Practice

- How should be managed thyroid nodules in pregnancy?
- Is the prognosis of thyroid carcinoma worse in pregnancy?
- What is the optimal timing for thyroid surgery and radioiodine ablation?
- What is the effect of pregnancy on the risk of thyroid carcinoma recurrences?

The effect of pregnancy on thyroid nodule formation

Kung et al, JCEM 2002, 87: 1010-14



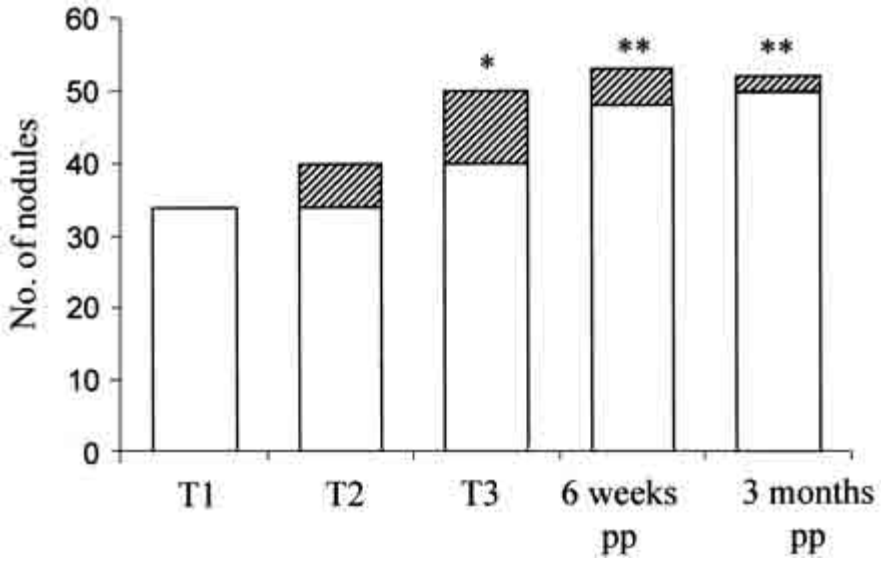
Number of thyroid nodules at each stage of pregnancy and in postpartum

(*P<0.05, **P<0.02)

Prospective study on 221 women

Changes in the volume of dominant nodule detected at various stages of pregnancy and postpartum

(*P<0.05, **P<0.02,***P<0.001 vs



Fine-needle aspiration of thyroid lesions in 57 pregnant and postpartum women

Marley EF, Oertel YC. Diagn Cytopathol. 1997; 16: 122-5.

- 97 thyroid nodules. Cytologic diagnoses: 31 benign, 7 adenomatoid, 5 suspicious, 12 papillary carcinomas, and 2 follicular neoplasms
- Lesions present before pregnancy did not show "progression" or change
- No characteristic features ascribable to pregnancy were identified
- Standard diagnostic criteria may be used in FNA of thyroid nodules from pregnant patients.

Is the prognosis of thyroid carcinoma worse in pregnancy?

Thyroid cancer and pregnancy: prognosis

- 61 women with DTC discovered in pregnancy vs. 598 matched women diagnosed out of pregnancy (retrospective cohort study)
- 87% papillary TC; 13% follicular TC
- Stage: 13% stage 1 (<1.5 cm); 69% stage 2 (1.5-4.4 cm or lymph node metastases); 16% stage 3; 2% stage 4
- Tumor size, local or distant tumor invasion: NS
- Time to initial therapy: 12.7 mo. in pregnant vs. 10.8 in not pregnant ones (NS).

Moosa et al, JCEM 1997, 82: 2862-26

Outcome in pregnant women with DTC (2)

Outcome	Pregnant	Not Pregnant
Recurrence (yrs)		
10	8 (15%)	85 (21%)
20	1 (17%)	13 (26%)
30	0 (17%)	8 (31%)
40	0 (**17%**)	1 (**33%**)
Distant recurrence (yrs)		
10	1 (2%)	9 (2%)
20	0 (2%)	1 (3%)
30	0 (**2%**)	2 (**4%**)
Cancer death (yrs)		
10	0	0
20	**0**	2 (**1%**)

Moosa M & Mazzaferri EL. JCEM, 1997; 82: 2862-6

Thyroid Cancer in pregnancy

Maternal and newborn records linked to California Cancer Registry were queried on all thyroid cancers from 1991 to 1999

595 cases

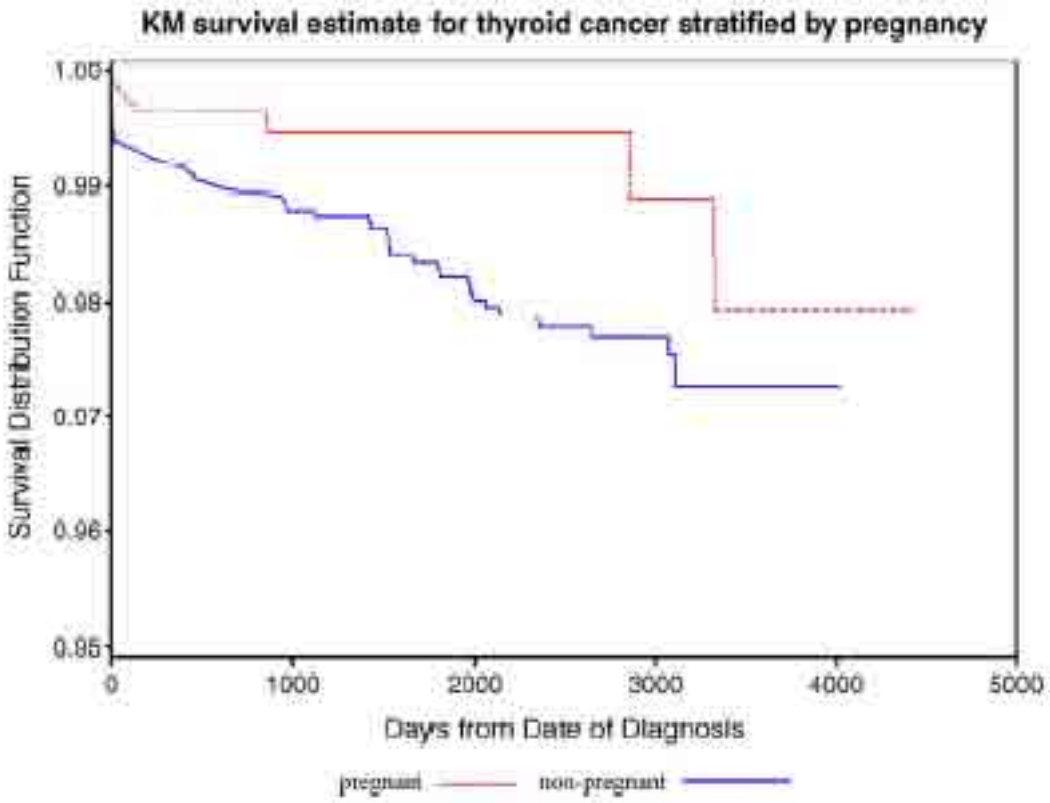
Diagnosis: 129 antepartum *and* 466 12 months postpartum

78% had surgery during pregnancy

22% had surgery after delivery

Yasmeen S. Int J Gynaecol Obstet 2005; 91:15-20

Thyroid cancer in pregnancy: survival (2)



Pregnancy had no significant effect on mortality due to thyroid cancer

Thyroid cancer and pregnancy: prognosis

- A good outcome for differentiated thyroid cancer in pregnant women is expected.

  Vini L et al, Eur J Endocrinol 1999; 140: 404-406.

- The greater prevalence of cervical node metastases in papillary carcinoma during pregnancy doesn't alter the final prognosis.
- After delivery, papillary cancer shows the same behavior in both groups.

  Monroy-Lozano et al, Ginecol Obstet Mex 2001; 69: 359-362;
  Nam KH, et al. J Surg Oncol 2005; 91: 199-203.

Pregnancy and DTC outcome

Vannucchi et al, EJE 2009

	Group 1 n= 47 (%)	Group 2 n= 15 (%)*	Group 3 n= 61 (%)	P value
Age at diagnosis (mean ±SD)	36.1±5.3	32.3±6.4	34.1±6.2	0.08
Months of follow-up (mean±SD)	68.2±63.9	60.1±52.1	64.7±43.5	0.92
pTNM				
T1	18/47 (38.3)	5/15 (33.3)	20/61 (32.8)	0.97
T2	9/47 (19.1)	2/15 (13.3)	12/61 (19.7)	
T3	19/47 (40.4)	7/15 (46.6)	27/61 (44.3)	
T4	1/47 (2.1)	0/15 (0)	2/61 (3.3)	
NX	15/47 (31.9)	3/15 (20)	18/61 (29.5)	0.44
N0	12/47 (25.5)	2/15 (13.3)	18/61 (29.5)	
N1	20/47 (42.5)	10/15 (66.6)	25/61 (40.9)	
Papillary histotype**	46/47 (97.8)	12/15 (80)	60/61 (98.3)	**<0.0001[a]**
Radioiodine ablation	38/47 (80.8)	15/15 (100)	53/61 (86.9)	0.17
^{131}I MBq (mean±SD)	3826±2053	5602±5975	4912±3873	0.31
ERα tumor expression	5/16 (31)	7/8 (87.5)	0/14	**0.01[b]**
Persistence	2/47 (4.2)	9/15 (60)	8/61 (13.1)	**<0.0001[c]**

DTC diagnosed during pregnancy was associated with a poorer prognosis compared to tumors not developed in pregnancy (P<0.0001).

ERα expression significantly differed among tumors of the three groups

Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features

Ilaria Messuti*, Stefania Corvisieri*, Francesca Bardesono, Ida Rapa[1], Jessica Giorcelli[1], Riccardo Pellerito[2], Marco Volante[1] and Fabio Orlandi

Remission	150/152 (98.7%)	34/38 (89.5%)	143/150 (95.3%)	0.023[a]
Persistence/recurrence	2/152 (1.3%)	4/38 (10.5%)	7/15 (4.7%)	
Number of treatments (average)	1.19	1.21	1.28	0.22
Ablation-HTG				
<10 ng/ml[b]	127/152 (83.5%)	27/38 (71%)	110/150 (73.3%)	0.060
>10 ng/ml[b]	25/152 (16.5%)	11/38 (29%)	40/150 (26.7)	
High risk	68/152 (44.7%)	19/38 (50%)	79/150 (52.7%)	0.38
Low risk	84/152 (55.3%)	19/38 (50%)	71/150 (47.3%)	
TNM				
T<3	105/152 (69%)	26/38 (68.4%)	95/150 (63.3%)	0.85
T>3	47/152 (31%)	12/38 (31.6%)	55/150 (36.7%)	
N−	114/152 (75%)	29/38 (76.3%)	102/150 (68%)	0.54
N+	38/152 (25%)	9/38 (23.6%)	48/150 (32%)	

Persistence/recurrence of disease was higher in group 2 patients than control groups (P=0.023).

No significant differences in other clinical parameters.

No differences about ER pattern, NIS expression, and BRAF mutations.

European Journal of Endocrinology (2014) 170, 659–666

Prognosis of thyroid cancer discovered during pregnancy

Study	No of patients / controls	Results
Herzon 1994	22 / 464	No difference in the 12-years survival rate
Moosa, 1997	61 / 528	DTC in pregnancy is similar for recurrence and survival to that occurring in non-pregnant women of similar age
Vini, 1999	9	Good outcome for DTC in pregnant women
Monroy-Lozano, 2001	6 / 24	No statistical differences in prognostic score, recurrence, mortality (follow-up 20-25 yrs), no local recurrence. The greater prevalence of cervical nodes metastasis in papillary cancer diagnosed during pregnancy does not alter the final prognosis
Jasmeen, 2005	129 / 466	Women with DTC in pregnancy and age-matched non-pregnant DTC controls had NS difference in recurrence and survival rates
Nam, 2005	15	No local recurrence and no distant metastasis
Vannucchi 2010	15 / 61	Pregnancy has a negative impact on the outcome of DTC both in terms of persistence or relapse disease. The presence of ERα in the majority of tumors diagnosed during pregnancy indicates that the poorer outcome could be estrogen-related

Papillary Thyroid Microcarcinoma Might Progress During Pregnancy

Hisakazu Shindo,[1] Nobuyuki Amino,[2] Yasuhiro Ito,[1] Minoru Kihara,[1] Kaoru Kobayashi,[1] Akihiro Miya,[1] Mitsuyoshi Hirokawa,[3] and Akira Miyauchi[1]

Tumor size at diagnosis (mm)			
Mean ± SD	6.4 ± 1.8	6.6 ± 1.9	0.747
Range	3–9	4–10	
Tumor size at last exam (mm)			
Mean ± SD	9.6 ± 5.0	7.3 ± 2.1	0.058
Range	4–18	3–13	

PTMC enlargement occurred in 44.4% (4/9) of the pregnant subjects, whereas it occurred only in 11.1% (3/27) of the controls

THYROID
Volume 24, Number 5, 2014

Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital

Yasuhiro Ito, Akira Miyauchi, Takumi Kudo, Hisashi Ota, Kana Yoshioka, Hitomi Oda, Hisanori Sasai, Ayako Nakayama, Tomonori Yabuta, Hiroo Masuoka, Mitsuhiro Fukushima, Takuya Higashiyama, Minoru Kihara, Kaoru Kobayashi, and Akihiro Miya

TABLE 1. CHANGE IN THE SIZE OF 50 PMC CASES FROM BEFORE PREGNANCY TO AFTER DELIVERY

Size change	*≥3 mm*	*+2 mm*	*+1 mm to −1 mm*	*−2 mm*	*−3 mm*	*Total*
No. of patients	4 (8%)	1 (2%)	44 (86%)	1 (2%)	1 (2%)	51 (100%)

PMC, papillary microcarcinoma.

Four patients (8%) showed enlargement of PMC by ‡3 mm and 44 patients (90%) showed stable disease.
None of the patients had a novel lymph node metastases during pregnancy.

THYROID
Volume 26, Number 1, 2016

MOLECULAR AND CLINICAL ONCOLOGY 3: 341-346, 2015

Association of thyroid carcinoma with pregnancy: A meta-analysis

Y.Q. ZHOU, Z. ZHOU, M.F. QIAN, T. GONG and J.D. WANG

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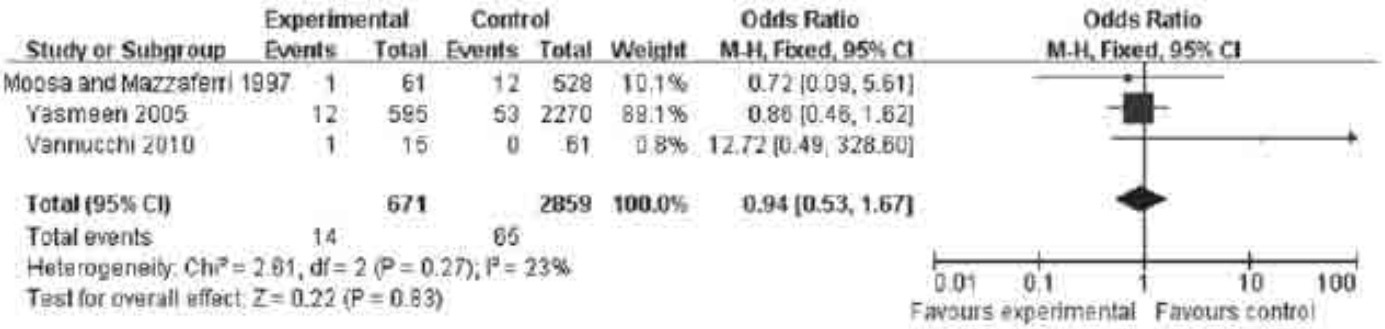


Figure 5. Meta-analysis of the association between thyroid carcinoma during pregnancy and distant metastasis. Total odds ratio = 0.94 (95% CI: 0.53-1.67), indicating that pregnancy did not increase the distant metastasis rate. CI, confidence interval.

Patients who developed thyroid cancer during pregnancy did not exhibit an increased risk of lymphatic metastasis (OR=0.94)

The risk of distant metastasis also did not increase significantly OR=1.03)

What is the optimal timing for thyroid surgery and radioiodine ablation?

Side effects of surgery during pregnancy

Study	% patients operated during 2nd trimester	Side effects: mother	Side effects: fetus
Cunningham, 1970	-	-	3 / 5
Rosen, 1986	8	0 / 2	0 / 2
Herzon 1994	27	-	0 / 6
Doherty, 1995	36	0 / 4	0 / 4
Tan, 1996	33	0 / 4	0 / 4
Moosa, 1997	20	-	-
Vini 1999	11	0 / 1	0 / 1
Nam 2005	40	0 / 6	0 / 6
Jasmeen, 2005	78	0 / 96	0 / 96
Chong, 2007	-	0 / 2	0 / 2
Total		0 / 115	3 / 126

Outcome in patients operated during pregnancy

Moosa M. and Mazzaferri E.L., JEC&M 1997; 82: 2862-2866

	Surgery during pregnancy	Surgery after delivery	*P*
Age (years)	23.7 ± 4.7	26.7 ± 6.1	NS
Time (months)	1.1 ± 1.0	16.1 ± 19.7	0.001
Tumor D (cm)	2.0 ± 1.2	2.6 ± 1.6	NS
Nodal metastases			
None	**10 (71 %)**	**26 (55 %)**	**NS**
Unilateral	2 (14 %)	16 (34 %)	NS
Bilateral	2 (14 %)	4 (9 %)	NS
Mediastinal	0	1 (2 %)	NS
Recurrence	**2 (14 %)**	**7 (15 %)**	**NS**
Distant recurrences	**0**	**1 (2 %)**	**NS**

Timing of surgery does not affect prognosis

- No difference in recurrence or survival noticed between women treated during or after delivery.

  Moosa et al, JCEM 1997; 82: 2862-6.

- A pregnant patient with papillary cancer can wait the end of pregnancy for treatment.

  Monroy-Lozano et al, Ginecol Obstet Mex 2001; 69: 359-362

- Women treated for DTC after delivery showed a slight increase in tumor size during pregnancy, without affecting prognosis.

- No significant difference in outcome between surgery performed after delivery or during 2nd trimester of pregnancy.

  Nam KH, et al. J Surg Oncol 2005; 91:199-203

Thyroid cancer in pregnancy: side effects

Yasmeen S. Int J Gynaecol Obstet 2005; 91:15-20

database containing maternal and newborn records linked to the California Cancer Registry was queried on all thyroid cancers from 1991 to1999

Diagnosis: 129 antepartum

78% had surgery **during** pregnancy

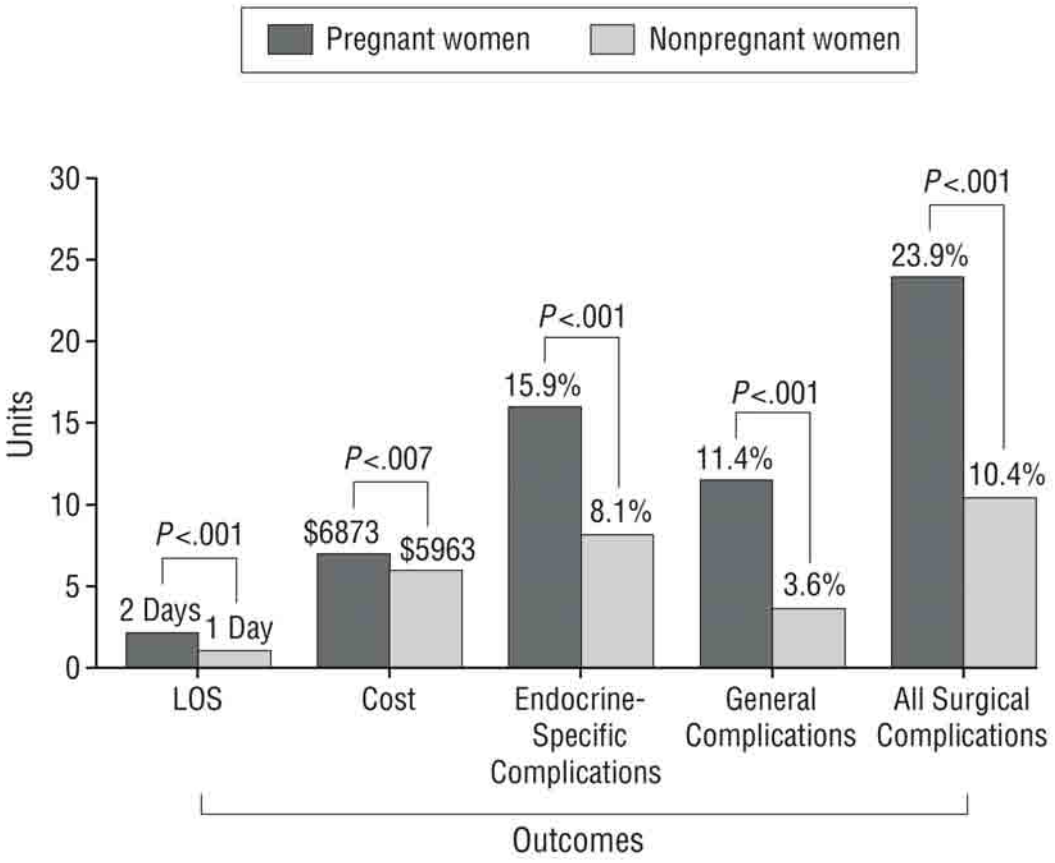
22% had surgery **after** delivery

Thyroidectomy during pregnancy was not associated with adverse maternal or neonatal outcomes

Outcomes Following Thyroid and Parathyroid Surgery in Pregnant Women

SreyRam Kuy, MD; Sanziana A. Roman, MD; Rani Desai, PhD; Julie Ann Sosa, MA, MD

Arch Surg. 2009;144(5):399-406



- The fetal and maternal complication rates were 5.5% and 4.5%, respectively.
- On multivariate regression analysis, pregnancy was an independent predictor of:
  - Higher surgical complications (OR, 2)
  - longer adjusted length of stay (0.3 days)
  - higher adjusted hospital costs ($300)
- Other independent predic tors of outcome were surgeon volume, patient race or ethnicity, and insurance status.

Optimal Timing of Surgery for Differentiated Thyroid Cancer in Pregnant Women

Takashi Uruno · Hiroshi Shibuya · Wataru Kitagawa · Mitsuji Nagahama · Kiminori Sugino · Koichi Ito

- 45 patients with DTC operated on during pregnancy or within 1 year after delivery
- No complications with surgery or general anesthesia in either group
- No differences in terms of tumor size, lymph node metastasis, or extrathyroidal extension. No distant metastases
- Two small for date infants (8.3 %) and 2 heavy for date infants (8.3%) in group A, 1 small for date infant (4.7 %) in group B
- No miscarriages and no birth defects.

World J Surg (2014) 38:704–708

Outcome of pregnancy and radioiodine exposure

Chow S, et al. Int J Radiation Oncology Biol Phys 2004; 59: 992-1000

Characteristic	RAI dose		Interval RAI-pregnancy	
	<80 mCi	>80 mCi	<1 yr	>1 yr
Pregnancies (n)	**95**	**21**	**15**	**101**
Live births	**64 (67.4%)**	**14 (66.7%)**	**7 (46.7%)**	**71 (70.3%)**
Induced abortion	**20 (21.1%)**	**4 (19%)**	**8 (53.3%)**	**16 (15.8%)**
Miscarriage	**11 (11.6%)**	**2 (9.5%)**	**0**	**13 (12.9%)**
Birth weight (mean, kg)	**3.3±0.5**	**3.2±0.5**	**3.4±0.5**	**3.3±0.5**
Preterm delivery	**5 (7.8%)**	**2 (14.3%)**	**1 (14.3%)**	**6 (8.5%)**
First year neonatal mortality	**0**	**0**	**0**	**0**

A 1-yr interval after high dose RAI was not associated with adverse outcome

A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors

Anna M. Sawka*,†, Deepak C. Lakra‡, Jane Lea§, Bandar Alshehri¶, Richard W. Tsang**,††, James D. Brierley**,††, Sharon Straus‡‡,§§, Lehana Thabane¶¶,***, Amiram Gafni¶¶,†††, Shereen Ezzat†,‡‡‡,§§§,¶¶¶, Susan R. George*,† and David P. Goldstein****

- 16 observational studies reporting data from:
  - 3023 women
  - 591 pregnancies
  - 496 live births
- Age at first RAI treatment: 8 - 50 years
- Cumulative activities of RAI administered: 30 to 1099 mCi

Transient absence of menstrual periods within the first year,
Treatment with RI NOT associated with increased risk of infertility, miscarriage, stillbirths, neonatal mortality and malformations.

Clinical Endocrinology 2008

A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors

Anna M. Sawka et al. Clinical Endocrinology 2008; **69 :** 479–490

- Clinical guidelines recommend that women treated with RAI **wait at least 6–12 months** before conceiving
- Although there is a paucity of evidence, clinical practice recommendations are reasonable, given the potential for increased risk of miscarriage or induced abortion within the first year after RAI treatment and the need for optimization of levothyroxine dosing
- Beyond the first year after RAI treatment, **no** evidence that RAI treatment for DTC results in an increased risk of adverse events in future pregnancies.

Reproductive Outcomes and Nononcologic Complications After Radioactive Iodine Ablation for Well-Differentiated Thyroid Cancer

James X. Wu,[1] Stephanie Young,[1] Kevin Ro,[1] Ning Li,[2] Angela M. Leung,[3] Harvey K. Chiu,[4] Avital Harari,[1] and Michael W. Yeh[1]

A retrospective cohort study of 18,850 women with WDTC using the California Cancer Registry

Delay to first live birth was observed ($p < 0.05$)

The only nononcologic adverse effect associated with RAI ablation was an increased rate of nasolacrimal stenosis (RR 3.44).

THYROID
Volume 25, Number 1, 2015

What is the effect of pregnancy on the risk of thyroid carcinoma recurrences?

The effect of a subsequent pregnancy on patients with thyroid carcinoma

- None of 38 women disease-free before pregnancy relapsed during or after pregnancy.

  Rosvoll RV & Winship T. Surg Gynecol Obstet 1965; 121: 1039-42

- No difference in the recurrence rate between 70 women who became pregnant after diagnosis of DTC and 109 patients who did not.

  Hill CS et al. Surg Gynecol Obstet 1966; 122: 1219-22

- None of 23 patients disease-free relapsed before or during pregnancy.

  Pomorski L et al. Zentralbl Gynakol 2000; 122: 383-86

The effect of a subsequent pregnancy on patients with thyroid carcinoma apparently free of the disease

Rosario PW et al. Thyroid 2007, 17: 1175-76

- 78 pregnancies of 66 patients with a mean disease-free period of 30 months after thyroidectomy and ^{131}I ablation
- All patients presented Tg on T4 < 2 ng/ml with a negative neck US
- The clinical exam and US continued to be normal in all patients during pregnancy
- Six months after delivery serum Tg values were stable or showed a > 20% reduction.

Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer

Leboeuf R et al. Thyroid 2007, 17: 543-47

- 36 patients with differentiated thyroid cancer who became pregnant a median of 4.3 years after initial therapy (total thyroidectomy and ^{131}I ablation in 23 only).
- Eight women had Tg values on LT4 after delivery more than 20% higher than pre-pregnancy levels
- Among the 3 patients with metastases before pregnancy, one presented an increase in lymph node size and one a marked Tg level increase
- None of the patients with negative imaging exams and “low” Tg levels (< 3.2 ng/ml) relapsed.

Pitfalls: lack of US examination in most cases, TSH not monitored during pregnancy, various modality of treatment.

So, which are the Conclusions?

Thyroid Nodule Management

- Manage thyroid nodules for pregnant women in the same way as for non pregnant women *[GRADE A]*

- When suspicious clinical or US findings are present, we recommend UGFNA since cytologic diagnostic criteria are not substantially influenced by pregnancy *[GRADE A]*

Radioactive Agents

- Use of radioactive agents for diagnostic, as well as therapeutic, purposes is contraindicated *[GRADE A]*

- In the case of subnormal TSH levels during the second half of pregnancy, postpone radionuclide thyroid scan until after delivery and cessation of breast-feeding *[GRADE A]*

Fine Needle Aspiration

- For thyroid nodules that grow substantially or become symptomatic during pregnancy, follow-up with US examination is recommended, and if appropriate, UGFNA is recommended also *[GRADE A]*

- If UGFNA shows indeterminate cytologic findings, we recommend US monitoring and postponing surgery until after delivery *[GRADE B]*

- L-T4 suppressive therapy is not recommended while iodine supplementation is strongly suggested in iodine- deficient regions *[Grade A].*

Thyroid Carcinoma: Surgery

- When thyroid malignancy is diagnosed during the first or second trimester, thyroidectomy may be performed during the second trimester *[GRADE B]*

- For women with clinical or US evidence of extracapsular growth or lymph node metastases, consider surgical treatment during the second trimester of pregnancy *[GRADE B].*

Thyroid Carcinoma: Monitoring

- Women without evidence of aggressive thyroid cancer should be reassured that surgical treatment performed soon after delivery is unlikely to adversely affect the prognosis

- Close clinical and US monitoring is recommended [*GRADE B*]

Thyroid Carcinoma: Delayed Surgery

- When thyroid malignancy is diagnosed during the third trimester, in absence of aggressive findings, surgical treatment can be deferred until the immediate postpartum period *[GRADE C]*
- For women with suspicious or malignant thyroid nodules in whom surgery is postponed until after delivery, we suggest maintenance of TSH at low-normal levels (about 0.5 mIU/L) *[GRADE B]*

Thyroid Carcinoma: RAI Therapy

- After surgery, RAI therapy should not be given to women with DTC who are still breast-feeding.
- Breast feeding should be stopped by at least 6-8 weeks before RAI. Dopaminergic agents may be useful.
- RAI treatment may be deferred until 12 months after surgery, unless in presence of aggressive or advanced disease
- Pregnancy is safe after 12 months and should always be delayed for at least 6 months *[Grade A]*.

So, we have just to think and make the best possible choice all together !