

Gynecologic Cancer and Pregnancy— The 2008 Consensus Statements

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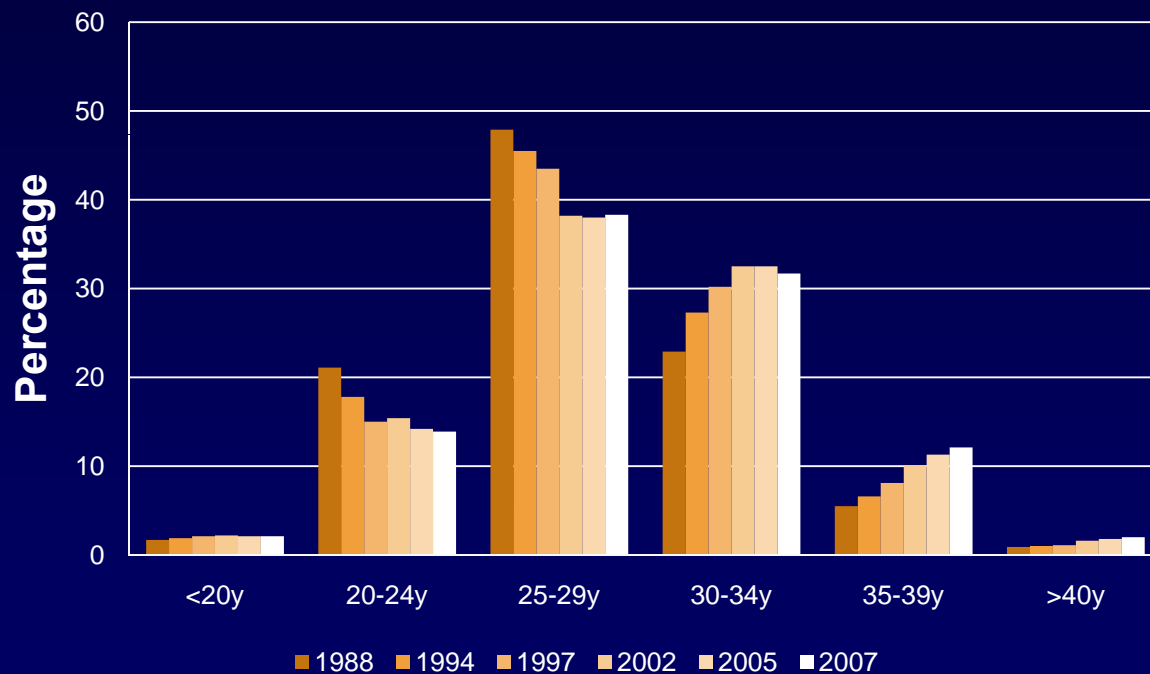


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Flemish Study Center Perinatal Epidemiology (SPE)

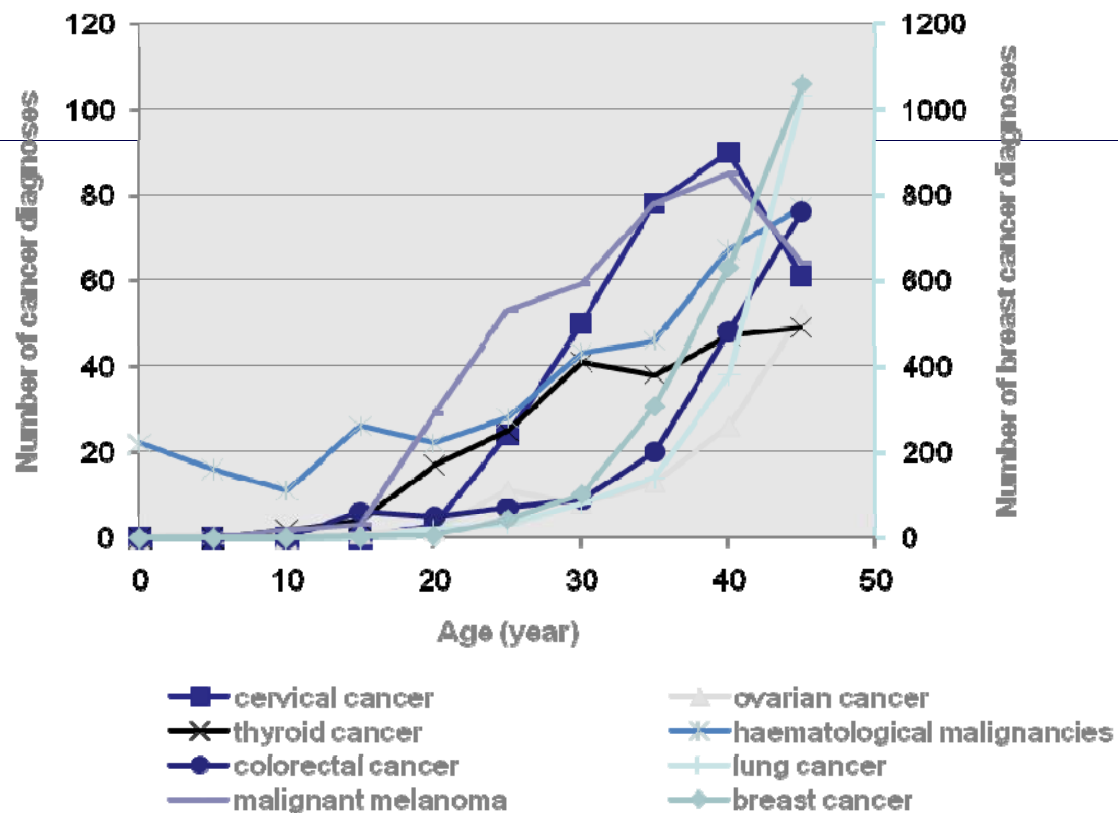
Distribution of maternal age at delivery in Flanders



Yearly, more than 5 million children are born in Europe and it is estimated that in 2500-5000 of them the pregnancy is complicated by cancer.

Incidence Cancer Types Per Age in Belgium (FOD, economy)

Incidence of cancer types per age in Belgian women in 2004



Cause Specific Survival of Cancer During P or PP

		n	Cause-Specific Death	
			Deaths	HR (95% CI)
All	Reference	41464	12965	1
	Pregnant	516	133	1.03(0.86 – 1.2)
	Lactating	531	135	1.02 (0.86 - 1.2)
Breast ca	Pregnant	59	26	1.23 (0.83-1.81)
	Lactating	46	31	1.95 (1.36-2.78)
Ovarian ca	Pregnant	38	4	0.46 (0.17-1.23)
	Lactating	15	7	2.23 (1.05-4.73)
Cervical ca	Pregnant	80	14	0.89 (0.52-1.53)
	Lactating	111	15	0.94 (0.56-1.57)

Chemotherapy

All-or-nothing

17% congenital anomalies

- Nasal and auditory canal abnormalities
- Micrognathia
- Limb deformities

Exclusion of folate antagonists:
6% (\leftrightarrow 3% general population)

IUGR?
Premature birth?
(IUD)

Conception

10 days

10 w

40 w

Radiotherapy

All-or-nothing

10cGy

IUGR
Central nervous system
Microcephaly
Eye anomalies
Mental retardation

Slight increase leukemia
during childhood
0.003-0.004 (nl 0.002-0.003)

2-4 week 'safety period' \rightarrow start treatment from 12-14 weeks of pregnancy

Approximate Fetal Absorbed Doses During Imaging Studies

The threshold dose for fetal damage is estimated to vary between 10-20 cGy

Procedure	Fetal Dose, cGy	Procedure	Fetal Dose, cGy
Chest x-ray (PA&lateral)	0.00006	Lumbosacral spine	0.2 – 0.6
Abdominal x-ray	0.15 – 0.26	Mammography	0.01 – 0.04
Pelvic x-ray	0.2 – 0.35	CT thorax	0.01 – 1.3
Intravenous pyelography	0.4 – 0.9	CT abdomen	0.8 – 3
Barium enema	0.3 – 4	CT pelvis	2.5 – 8.9
Dorsal spine	<0.001	Tc bone scan	0.15 – 0.20
Lumbar spine	0.4 – 0.6		

Sonography and magnetic resonance imaging are considered safe and preferred, especially for the abdomen or pelvis

Review on 12.452 Surgical Cases During Pregnancy

Outcome	n	N	%
Miscarriage - All trimesters	236	4069	5.8
- 1 st trimester	43	411	10.5
Elective termination	23	1770	1.3
Major congenital malformation			
- All trimesters	194	9878	2.0
- 1 st trimester	105	2663	3.9
Fetal loss - Overall	40	1536	2.5
- Perforated appendix	18	182	10.9
Surgery-induced premature delivery	79	2282	3.5
Prematurity	597	7313	8.2

Open Laparoscopy for Benign Disease During Pregnancy

Mathevet et al.¹

- N = 48
 - 1st trim: 17
 - 2nd trim: 27
 - 3rd trim: 4 (<33 w)
- Conversion: 2
- 1 fetal loss after 4 days (17 w cystectomy)
- 3 oral tocolytics after several weeks
- **Safe and effective in experienced hands**

Yuen et al.²

- N = 67
- Mean gestational age at surgery: 16 w
- Conversion: 2
- 1 spontaneous abortion after 6w
- No tocolytic, no complications
- **Safe and effective in experienced hands**

Recommendations for Maternal and Fetal Surveillance When Pregnant Women Are Operated

Anesthesia	Position pregnant patients in left lateral tilt Prevent hypoxia, hypotension, and hypoglycemia Adequate postoperative analgesia
Fetal monitoring	Screening ultrasonography before surgery Assessment fetal well-being immediately presurgery and postsurgery
Uterine monitoring	Presurgery and postsurgery
Lung maturation	Dexamethasone or betamethasone 24 hours before interventions between 24-34 weeks
Tocolytic drugs	Case-related: To be discussed with obstetrician Consider when uterine manipulation is expected Should be started in case of preterm labor
Thrombosis prophylaxis	Low molecular weight heparin recommended
Laparoscopy	Open technique Limit pressure (max 15 mmHg) and time (<90 min) of pneumoperitoneum

Safety of Sentinel Node During Pregnancy

➤ 18.5 MBq ^{99m}Tc safe in patients with breast cancer

- Fetal dose <0.05 mGy (threshold is 100 mGy)
- Low dosages
- Capture of ^{99m}Tc in lymph nodes
 - Keleher et al. *Breast J.* 2004¹
 - Gentilini et al. *Ann Oncol.* 2004²

➤ 60-80 MBq safe in vulvar cancer

- 80% remains in injection site or lymph nodes
- Distance to fetus at least 10 cm
- Fetal exposure for 100 MBq is around 0.1 mGy, ie, 1000 times lower than threshold of 100 mGy
 - Personal communication Ate Van der Zee

➤ Patent blue is not recommended

- Anaphylactic reaction during pregnancy is hazardous

Physiologic Adaptations in Pregnancy: ADME

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

In the absence of valid data, standard height-weight based dosages of chemotherapy are administered in pregnant women

Taxanes During Pregnancy

- 20 cases retrieved from literature
 - 13 paclitaxel
 - 7 docetaxel
- 17/20 in combination
 - Serial (breast cancer)
 - Parallel (ovarian or lung cancer)
- Hydrocephalia after doce/doxo/cyclo but normal outcome after 28 months (Potluri V, et al. *Clin Breast Cancer*. 2006)
- Reassuring though overall short follow-up

de Santis M, et al. *Eur J Cancer Care (Engl)*. 2000;9(4):235-257. Sood AK, et al. *Gynecol Oncol*. 2001;83(3):599-600. Gadducci A, et al. *Anticancer Res*. 2003;23(6D):5225-5229. Méndez LE, et al. *Obstet Gynecol*. 2003;102(5Pt 2):1200-1202. Picone O, et al. *Gynecol Oncol*. 2004;94(2):600-604. Gonzalez-Angulo AM, et al. *Clin Breast Cancer*. 2004;5(4):317-319. Potluri V, et al. *Clin Breast Cancer*. 2006;7(2):167-170. Nieto Y, et al. *Clin Breast Cancer*. 2006;6(6):533-534. Gainford MC, et al. *Clin Oncol (R Coll Radiol)*. 2006;18(2):159. Lycette JL, et al. *Clin Breast Cancer*. 2006;7(4):342-344. Tabata T, et al. *Int J Gynecol Cancer*. 2008;18(1):181-184. Modares Gilani M, et al. *Int J Gynecol Cancer*. 2007;17(5):1140-1143. Kim JH, et al. *Lung Cancer*. 2008;59(2):270-273. Mantovani G, et al. *Eur J Obstet Gynecol Reprod Biol*. 2007;131(2):238-239. Hubalek M, et al. *Arch Gynecol Obstet*. 2007;276(2):179-183. Bader AA, et al. *Lancet Oncol*. 2007;8(1):79-81. Sekar R, et al. *Obstet Gynecol*. 2007;110(2Pt2):507-510. Garcia-Manero M, et al. *Eur J Surg Oncol*. 2009;35(2):215-218

Cisplatin During Pregnancy

- 37 cases retrieved from literature
- 1 case ventriculomegaly e causa ignota (BEP at 26 w, pelvic hematoma requiring transfusion)
 - Elit L, et al. *Gynecol Oncol.* 1999;72(1):123-127.
- 1 case moderate bilateral hearing loss (BEP, maternal sepsis, 1190g, respiratory distress, gentamicin neonatally)
 - Raffles A, et al. *Br J Obstet Gynaecol.* 1989;96(9):1099-1100.
- Short-term follow-up: 35/37 (95%) nl development

Bakri YN, et al. *Gynecol Oncol.* 1984;19(2):222-225. Raffles A, et al. *Br J Obstet Gynaecol.* 1989;96(9):1099-1100. Kim DS, et al. *Obstet Gynecol.* 1989;73(3 Pt 2):503-507. Horbelt D, et al. *Obstet Gynecol.* 1994;84(4 Pt 2):662-624. Elit L, et al. *Gynecol Oncol.* 1999;72(1):123-127. Malhotra N, et al. *Gynecol Oncol.* 2000;78(2):265-266. Otton G, et al. *Int J Gynecol Cancer.* 2001;11(5):413-417. Sood AK, et al. *Gynecol Oncol.* 2001;83(3):599-600. Cardonick E, et al. *Lancet Oncol.* 2004;5(5):283-291. Ferrandina G, et al. *Gynecol Oncol.* 2005;97(2):693-696. Han JY, et al. *Reprod Toxicol.* 2005;19(4):557-561. Caluwaerts S, et al. *Int J Gynecol Cancer.* 2006;16(2):905-908. Machado F, et al. *Gynecol Oncol.* 2007;105(2):446-450. Robova H, et al. *Int J Gynecol Cancer.* 2007;17(4):914-916. Kim JH, et al. *Lung Cancer.* 2008;59(2):270-273. Karimi Zarchi M, et al. *Arch Gynecol Obstet.* 2008;277(1):75-78. Palaia I, et al. *Am J Obstet Gynecol.* 2007;197(4):e5-6. Garrido M, et al. *Lung Cancer.* 2008;60(2):285-290.

Carboplatin During Pregnancy

- 8 cases retrieved from literature
 - 4 cases single agent
 - 4 cases in association with paclitaxel
- Normal neonatal outcome in all 8
- Short follow-up only (absence of congenital malformations or normal clinical examination)
- Given a better toxicity profile, carboplatin is preferred over cisplatin in pregnancy

Henderson CE, et al. *Gynecol Oncol.* 1993;49(1):92-94. Méndez LE, et al. *Obstet Gynecol.* 2003;102(5Pt2):1200-1202. Picone O, et al. *Gynecol Oncol.* 2004;94(2):600-604. Cardonick E, et al. *Lancet Oncol.* 2004;5(5):283-291. Hubalek M, et al. *Arch Gynecol Obstet.* 2007;276(2):179-183. Tabata T, et al. *Int J Gynecol Cancer.* 2008;18(1):181-184. Modares Gilani M, et al. *Int J Gynecol Cancer.* 2007;17(5):1140-1143.

Bleomycin-Etoposide-Cisplatin During Pregnancy

- 9 cases retrieved from literature
- 1 case ventriculomegaly e causa ignota (BEP at 26 w, pelvic hematoma requiring transfusion) (Elit L, et al. *Gynecol Oncol.* 1999;72(1):123-127.)
- 1 case moderate bilateral hearing loss (BEP, maternal sepsis, 1190 g, respiratory distress, gentamicin neonatally) (Raffles A, et al. *Br J Obstet Gynaecol.* 1989;96(9):1099-1100.)
- Short-term follow-up: 2/7 (29%) problems
- **Cisplatin-vinblastine-bleomycin or paclitaxel-carboplatin are advised**

Recommended Combinations of Chemotherapy in Nonpregnant and Pregnant Women

	Nonpregnant	Pregnant
Ovarian cancer		
Epithelial	Paclitaxel-carboplatin	Paclitaxel-carboplatin
Germ cell	Bleomycin-etoposide-cisplatin	Paclitaxel-carboplatin Cisplatin-vinblastine- bleomycin
Cervical cancer	Platin-based	Paclitaxel—cis/carboplatin

Most Important Supportive Drugs and Their Fetal Safety Profile

Supportive drugs	Fetal safety data
Antiemetics	
- Metoclopramide/alizapride	Metoclopramide can be used in all stages of pregnancy. Its methoxy-2-benzamide-derivate, alizapride, is probably also safe.
- 5-HT antagonists (granisetron, tropisetron, ondansetron)	Should not be withheld because of the pregnancy. Animal data suggest low risk. Case reports on ondansetron show its effectiveness in the control of vomiting in pregnancy and no adverse effects were observed in the children.
- NK1 antagonist (aprepitant)	Should not be withheld because of the pregnancy. No human data available, animal data suggest low risk.
- Corticoids	Can be used after the first trimester of pregnancy. Prednisolone or hydrocortisone are preferred
Growth factors	
Granulocyte colony-stimulating factors (pegfilgrastim, filgrastim, lenograstim)	Should not be withheld because of the pregnancy. Is crossing the placenta.
Erythropoetins	Should not be withheld because of the pregnancy. Is probably not crossing the placenta
Pain medication	
- Paracetamol	Drug of preference (untill 4 g/d)
- Nonsteroidal inflammatory drugs	Can be used between 12 and 32 weeks of gestation

MacDougall MK, et al. *Semin Oncol.* 2000;27(6):704-711. Siu SS, et al. *Hum Reprod.* 2002;17(4):1056-1059. Briggs GG, et al. *Ann Pharmacother.* 2008;42(6):898-901.

Monitoring Pregnancy

- Standard prenatal care
- Correct dating
- Carefull ultrasonographic screening before treatment to exclude pre-existing fetal anomalies
- Delay delivery untill 35-37 weeks
- **Prevention of prematurity**
- Lung maturation for deliveries <34 weeks

Long-Term Neonatal Outcome

- Prospective follow-up study of children who were *in utero* exposed to chemotherapy
- 58 children are included
- 43 children are >18 months and received standardized neurologic and cardiologic examination
- An interim analysis suggests no adverse events (1 member of a twin serious neurologic sequelae)

Evolution of Biopsy Proven Cervical Intraepithelial Neoplasia (CIN) During Pregnancy

	CIN 2-3, n	Persistent, %	Regression, %	Progression, %
Coppola, 1997 ¹	26	80	12	8
Yost, 1999 ²	71	30	70	0
Palle, 2000 ³	142	47	25	28 (n=2 microinvasive)
Vlahos, 2002 ⁴	78	38	62	0
Robova, 2005 ⁵	62	40	50	10
Ackermann, 2006 ⁶	77	63	34	2.4

1. Coppola A, et al. *Gynecol Oncol.* 1997;67(2):162-165. 2. Yost NP, et al. *Obstet Gynecol.* 1999;93(3):359-362. 3. Palle C, et al. *Acta Obstet Gynecol Scand.* 2000;79(4):306-310. 4. Vlahos C, et al. *Gynecol Obstet Invest.* 2002;54(2):78-81. 5. Robova H, et al. *Eur J Gynaecol Oncol.* 2005;26(6):611-614. 6. Ackermann S, et al. *Acta Obstet Gynecol Scand.* 2006;85(9):1134-1137.

CIN During Pregnancy

- If invasive disease can be ruled out, definitive therapy can be **deferred** until after delivery
- **Flat cone** if necessary
- **Vaginal delivery** is allowed in pre-invasive disease
- Vaginal delivery will not increase regression rates

Treatment of Cervical Cancer During Pregnancy

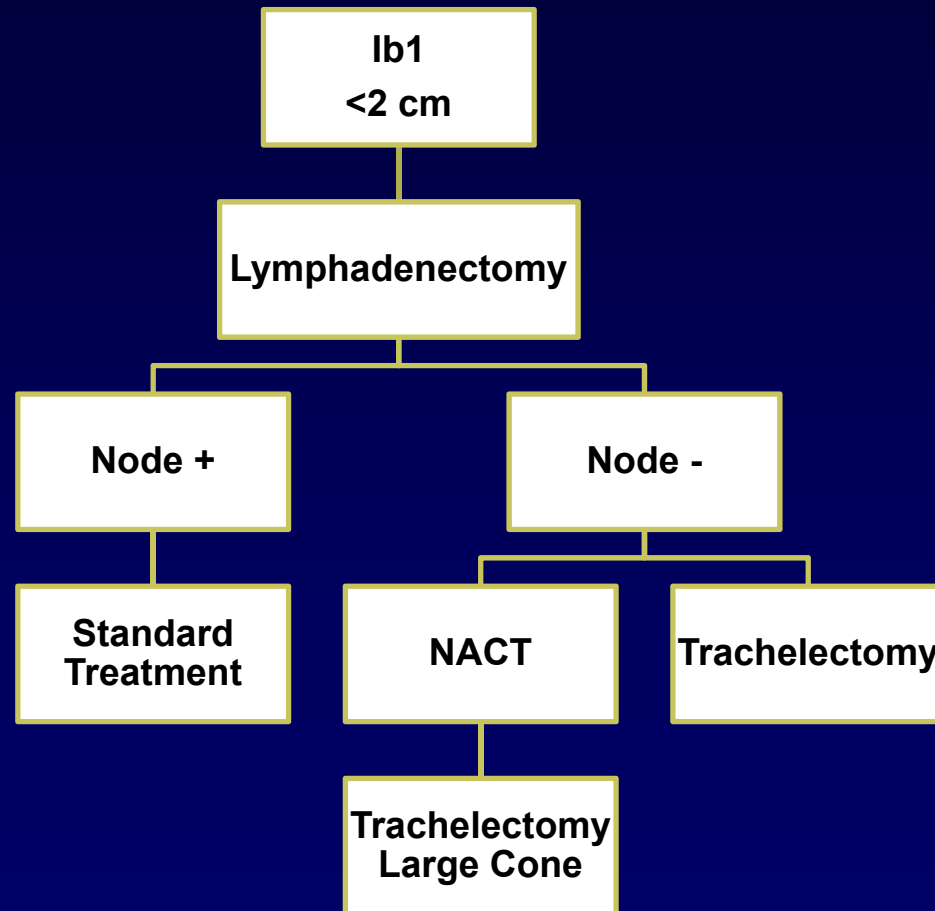
- Treatment during pregnancy is experimental
→ standard treatment is proposed
- Individualization!
- R/ according to trimester:
 - 1st: Await second trimester
 - **2nd: According to stage**
 - 3rd: Await fetal maturity

NACT for Cervical Cancer to Achieve Fetal Maturity

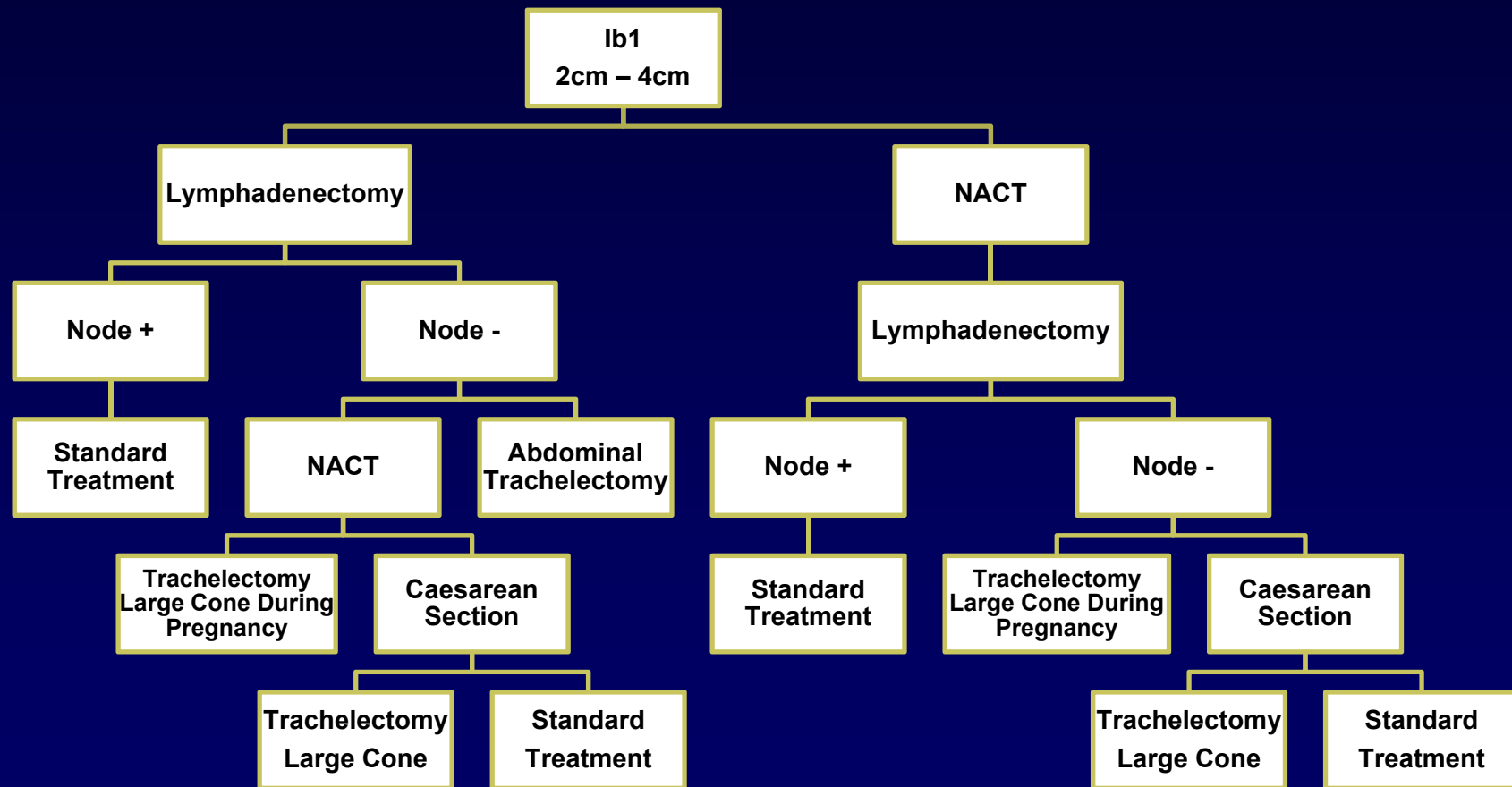
	Age	Stage	D/,w	CT	Surg, w	FU	Mother	Child
Giacalone, 1996 ¹	34	IB1	17	75 mg/m ² P (3 courses)	32	12	NED	NI
Tewari, 1998 ²	34	IIA	16	1 mg/m ² V, 50 mg/m ² P (6 courses)	34	5	DOD	NI
Tewari, 1998 ²	36	IB2	21	1 mg/m ² V, 50 mg/m ² P (4 courses)	32	24	NED	NI
Marana, 2001 ³	26	IIB	14	30 mg/m ² B, 50 mg/m ² P (2 courses)	38	12	DOD*	NI
Caluwaerts, 2006 ⁴	28	IB1	17	75 mg/m ² , P (6 courses)	32	10	NED	NI
Benhaim, 2006 ⁵	30	IIIB	22	50 mg/m ² P (2 courses)	28	10	DOD	NI
Palaia, 2007 ⁶	30	IIB	20	75 mg/m ² P (3 courses)	35	10	NED	NI
Karam, 2007 ⁷	28	IB2	23	40 mg/m ² P (6 courses)	33	14	NED	NI

1. Giacalone PL, et al. *Br J Obstet Gynaecol.* 1996;103(9):932-934. 2. Tewari K, et al. *Cancer.* 1998;82(8):1529-1534. 3. Marama HR, et al. *Gynecol Oncol.* 2001;80(2):272-274. 4. Caluwaerts S, et al. *Int J Gynecol Cancer.* 2006;16(2):905-908. 5. Benhaim Y, et al. *Eur J Obstet Gynecol Reprod Biol.* 2008;136(2):267-268. 6. Palaia I, et al. *Am J Obstet Gynecol.* 2007;197(4):e5-e6. 7. Karam A, et al. *Nat Clin Pract Oncol.* 2007;4(6):375-380.

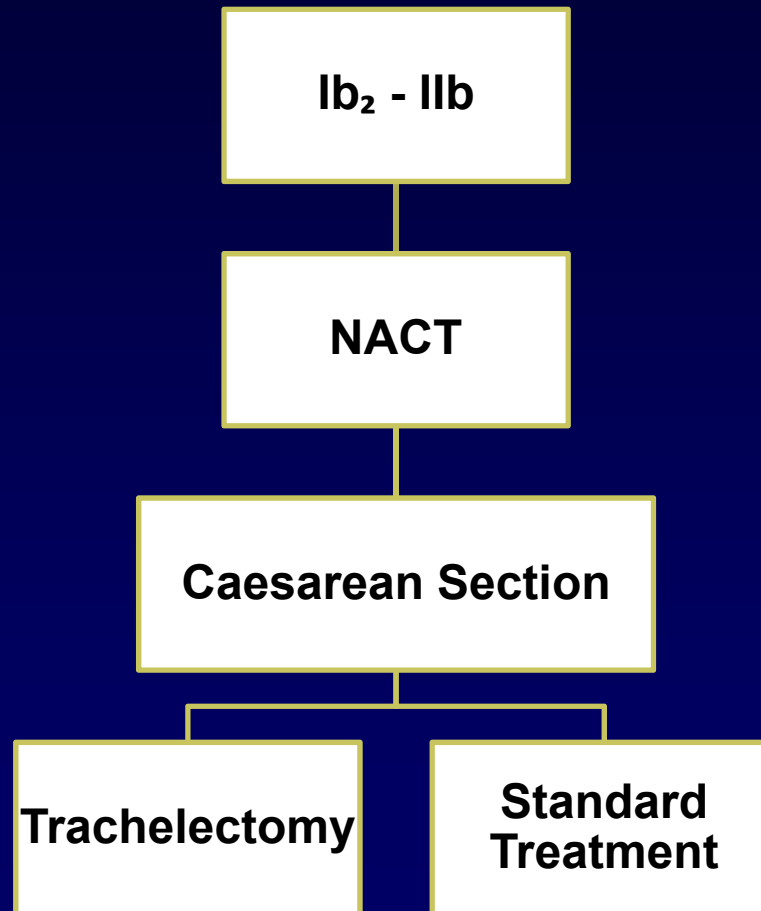
Algorithm for Treatment of Cervical Cancer Stage Ia2-Ib1, <2 cm Treated During the Second Trimester of Pregnancy in Patients Wishing to Preserve the Pregnancy and Fertility



Algorithm for Treatment of Cervical Cancer Stage Ib1, 2-4 cm Treated During the Second Trimester of Pregnancy in Patients Wishing to Preserve the Pregnancy and Fertility



Algorithm for Treatment of Cervical Cancer Stage Ib₂ – IIB Treated During the Second Trimester of Pregnancy in Patients Wishing to Preserve the Pregnancy and Fertility

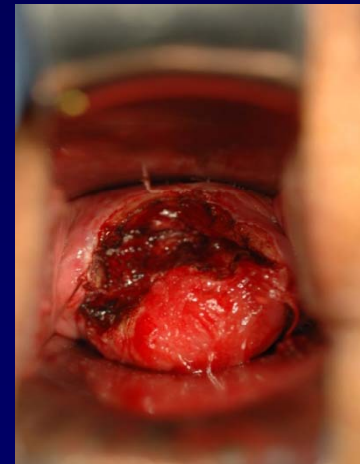
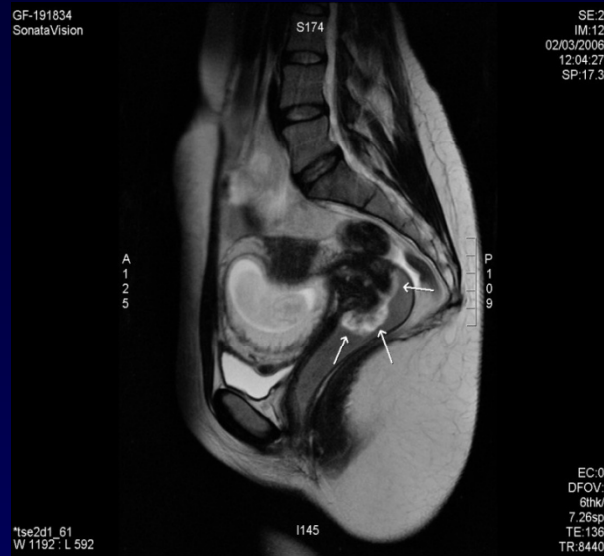


Episiotomy Site Recurrence After Vaginal Delivery (n = 13)

Author	Histology	Stage	DFS, months	R/ Recurrence	FU, months	Survival
Burgess & Waymont, 1987	Sq	IB	17	Exenteration		
Copeland, 1987	Adeno	IB	3	Surg, RT	>60	NED
	Adeno	IB	5	Surg, RT	10	NED
Gordon, 1989	Sq	IB	1	Surg, RT	42	NED
Van Dam, 1992	Sq	IIIA		Chemo		
Khalil, 1993	Adeno	IB	3	Surg, RT	>120	NED
Cliby, 1994	Sq	IIIB	3	Chemo, RT	4	DOD
	Sq	IB	2	Chemo	6	DOD
	Sq	IB	24	Chemo, surg, RT	12	NED
	Sq	IB	3	RT, exent	42	DOD
	Sq	IB	1	Surg, RT	6	DOD
Vandenbroek, 1995	Adeno	IA1	1.5	Surg	12	DOD
Goldman & Goldberg, 2003	Sq	IB	66	Surg, RT	>54	NED

Van Calsteren K, et al. *Best Pract Res Clin Obstet Gynaecol.* 2005;19(4):611-630.

Amputation Anterior Cervix for Adenoca Ib1



Van Calsteren K, et al. *Acta Obstet Gynecol Scand.* 2008;87(2):250-253.

Vulvar Cancer During Pregnancy

- **Node-negative disease**
 - R/ as in nonpregnant women
 - **Vulvar surgery**
 - Safe margins, no postoperative radiotherapy
 - Beware increased vascularisation
 - Discuss route of delivery with obstetrician
- **Node-positive disease**
 - 1st and 2nd trimester: TOP, standard R/
 - 3rd trimester: delivery followed by standard R/

Nonepithelial Ovarian Tumors During Pregnancy

- **Usually stage I: Staging (USO, omentectomy, peritoneal biopsies, cytology)**
- **Stage I grade 1 immature teratoma or stage I dysgerminoma: no further treatment**
- **Others: adjuvant paclitaxel-carboplatin**
- **Restaging after delivery based on tumor markers and imaging**

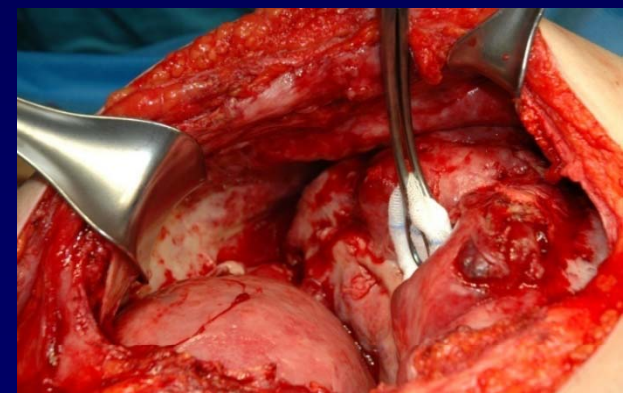
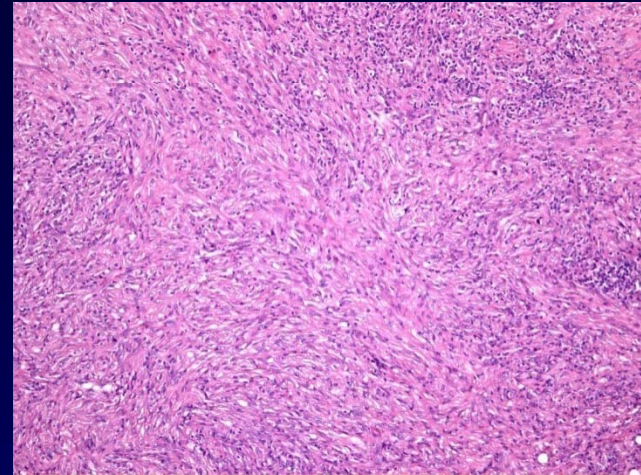
Borderline Ovarian Tumors During Pregnancy

- **Most likely to be stage I**
- **Staging including USO, omentectomy, peritoneal biopsies, cytology)**
- **Higher stages: Completion of staging after delivery**

Invasive Epithelial Ovarian Tumors During Pregnancy

- **Early-stage disease: staging +/- lymphadenectomy +/- chemotherapy**
- **Advanced stage (>I lb) disease:**
 - **<20 weeks: Preservation of pregnancy may be difficult**
 - **>20 weeks: Preservation is experimental**
 - **But possible:**
 - **Biopsy only (douglas inaccessible → incomplete debulking should be avoided during pregnancy)**
 - **NACT (paclitaxel-carboplatin)**
 - **Vaginal delivery and postpartal final surgery**

Undifferentiated High-Grade Sarcoma During Pregnancy: A Mutual Ominous Combination



Key Messages

Int J Gynecol Cancer 2009 May Issue

- **TOP** is unlikely to improve diagnosis
- **Maternal prognosis** probably similar to nonpregnant state
- Oncological surgery and chemotherapy **safe after 1st trimester**
- **Standard treatment** should be aimed for
- Prevention of **prematurity**
- No emergency, **take time** (for second opinion)