Cancer in Pregnancy

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1

1

Disclosures

No conflicts of interest

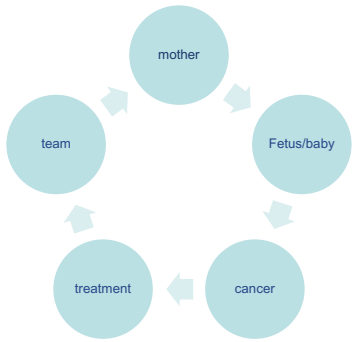
2

Objectives

- To review general diagnostic and therapeutic principles including systemic therapy for malignancies in pregnancy
  - Cervix
    - Dysplasia
    - Cancer
  - Ovary
    - Benign cysts
    - Ovarian malignancies
- To review the impact of a cancer diagnosis on the pregnancy and vice versa.

3

Expert knowledge



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Background

- Cancer in pregnancy is a rare circumstance with the co-incidence being 1:1,000 pregnancies.
  - » Reporting difficult as registries not linked
  - » Miscarriages or terminations may not be reported ->incidence underestimated
- 3,500-6,000 new cases of malignancies diagnosed in pregnancy in the U.S. annually.
- Incidence of cancer in pregnancy may be rising:
  - » Due to the increased delay in childbearing with corresponding increase in maternal age.
  - » Tends to increase in countries where there is non-invasive prenatal testing

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5

5

Background

- 20-30% of all malignant tumors emerge in women younger than age 45
- Population studies show no worse prognosis and no worse response to therapy in pregnant patients.
  - » Holds true for ovarian and cervical cancer

Table 1. Incidences gynecological cancers during pregnancy

Malignancy	Incidence (cases/pregnancies)	Comments
Cervical cancer	1.4–4.6 per 100 000	The variation in incidence during pregnancy is likely to reflect differences in underlying cervical incidence rates across population and screening programs.
Ovarian cancer	0.2–3.8 per 100 000	
Ovarian masses with low malignant potential	1.1–2.4 per 100 000	
Vulvar cancer	0.1 per 0.5 in 100 000	Rare, only 38 case reports in literature.
Vaginal cancer	0.1 per 0.5 in 100 000	Rare, only 12 case reports in literature.

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6

Diagnosis of Cancer in Pregnancy

- Diagnosis may be delayed as the pregnancy may mask the signs and symptoms of the malignancy.
  - » Cervical cancer may be the exception due to increased care.
- In general, most non-imaging based diagnostic procedures are considered safe during pregnancy.
- Radiographic diagnostics should be avoided if possible.
  - » Radiation effects on the fetus are dose-dependent and related to the stage of gestation.
  - » Should AVOID AXR, BEs, Abd CT, IVP, PET scan

7

Estimated fetal ionizing radiation dose from diagnostic imaging

Imaging technique	Fetal dose (mGy)	Rad
Cranial CT	<0.1	<0.01
CXR	<0.1	
Limb X-ray (not hips or pelvis)	<0.1	
Thoracic CT	1	0.1
Abdominal X-ray	3	0.3
Pelvic X-ray	6	0.6
IVP	6	0.6
Lumbar X-ray	7	0.7
CT abdomen/pelvis	30	3

8

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IVP	6	0.6
Lumbar X-ray	7	0.7
CT abdomen/pelvis	30	3

Keep dose < 100 mGy

9

Adverse effects of ionizing radiation on the fetus

Weeks of gestation	Effects	Est. Maximal dose mGy
Implantation (2-4)	SAB or no effects	50-100
Organogenesis (4-10)	-Congenital malformations	200
	-IUGR	200-250
Fetal period (10-17)	-Severe oligophreny	60-310
	-Microcephaly	200
Fetal period (18-27)	-Severe oligophreny	250-280

10

Nonionizing imaging procedures

- Ultrasound/MRI case be used at any gestational age
- Avoid Gadolinium
  - » No increase in congenital anomalies
  - » ? increased risk of rheumatologic, and dermatologic conditions, stillbirth
    - HR 1.36 for autoimmune conditions
    - HR 3.7 for stillbirths and neonatal deaths
- Newer MRIs have stronger magnets
  - » ? Effect of increasing amounts of tesla
- Pineapple juice as a contrast agent
  - » Contains manganese

JAMA. 2016;316(9):952-961
Acta Radiol Open 2017;6(9):

11

Systemic treatment in pregnancy

- Early exposure associated with a 10-20% risk of major malformations.
- Fetal benefit of treatment delay balanced against maternal risk.
- Ideal window is 14-35 weeks gestation
- Increased risk for IUGR, PPROM, preterm contractions

Table 3. Chemotherapy regimens used for cancer during pregnancy

Tumor type	Preferred regimen
Cervical cancer	Paclitaxel/carboplatin weekly or 3-weekly
Epithelial ovarian cancer	Paclitaxel/carboplatin 3 weekly
Nonepithelial ovarian cancer	(Bleomycine/) etoposide/cisplatin (BEP or EP)

BEP, bleomycin, etoposide and platinum; EP, etoposide and cisplatin.

Annals of Oncology 0: 1–12, 2019, *Lancet Oncology* 19: 337-46, 2018

12

Systemic treatment in pregnancy

- Small molecules and lipophilic agents trespass the placental barrier more easily.
- Strong placental drug-extruding transporters (PgP) inhibits placental transfer…may be specifically important for tubulin binding agents (paclitaxel, vinca-alkaloids).
- Plan on stopping 2-3 weeks before delivery
  - » Maternal neutropenia
  - » Fetal neutropenia
  - » Neonates have limited capacity to metabolize and eliminate drugs due to hepatic and renal immaturity

13

Monitoring during pregnancy

- Monitor q2-4 weeks
- Assess interval growth, amniotic fluid and cervical length (if appropriate)
- If IUGR, dopplers to evaluate fetal anemia via measurement of peak systolic velocity

14

Common Drugs

Chemotherapeutic Agent	Recommendations during pregnancy	
Methotrexate	Contraindicated	X
Anthracyclines	Safe in 2nd/3rd trimester	
Platinum derivatives	Carboplatin> cisplatin	
Taxanes	+/-	
5-FU	Safe in 2nd/3rd trimester	
Ifosfamide/cyclophosphamide	+/-	
Etoposide	+/-	
Bevacizumab	Contraindicated	X
Trastuzumab	Not recommended	X
Imatinib	Contraindicated	X
Anti-endocrine therapy	Contraindicated	X

15

Cervical Neoplasia and Pregnancy Screening and Management of Preinvasive Disease

- 4 million women will deliver in the U.S. each year
- 2-7% will have an abnormal pap smear during pregnancy
- Cervical cancer complicates 1-10/100,000 pregnancies each year

16

16

Diagnostic Procedures in Pregnancy

- Many physicians may feel reluctant to perform interventions during pregnancy
  - » Colposcopy may be more difficult due to increasing pelvic congestion
  - » Increase in vaginal wall protrusion and wall redundancy
  - » Changes in the pregnant cervix
  - » Increased bleeding
  - » Fear of related miscarriage
- These concerns should not lead to the omission of appropriate tests and follow up

17

17

Colposcopy and Biopsy

- Typically the cervix is everted by 20 weeks and most colposcopies should be adequate
- Use sidewall retractor or manipulate speculum to visualize the 4 quadrants
- Pregnancy related changes do NOT cause overestimation of lesion severity
  - » 83% correlation with CIN 1, 56% CIN2/3
  - » Concordance, overestimation, and underestimation of the final diagnosis in 72.6, 17.6, and 9.8 percent of cases, respectively

Eur J Obstet Gynecol Reprod Biol. 1995;62(1):31.
Am J Obstet Gynecol. 2010;203(2):113.e1.

18

18

Colposcopy and Biopsy

- Concerns over excess bleeding prevents physicians from performing biopsies
- Controversy in the literature
  - » Majority of the studies do not report increased bleeding complications or adverse pregnancy outcomes
- Beyond 1st trimester, cervical biopsy should be performed any time invasive cancer cannot be reliably excluded
- ECC is NOT appropriate during pregnancy and should not be performed
  - » One trial with 33 patients s/p ECC found that 97% delivered at term with no differences as compared to general population

Best Pract Res Clin Obstet Gynaecol. 2005;19(4):611 19

19

Pregnant women with LSIL

Colposcopy
- No CIN 2,3→post partum follow up
- CIN 2,3→ Manage per ASCCP guidelines

Regression of biopsy-proven HSIL in pregnancy ranging from 34% to 70%

Defer Colposcopy
- Wait at least 6 weeks post partum

Obstet Gynecol 1999 Mar;93[3]:359-62.
Acta Obstet Gynecol Scand 2006;85[9]:1134-7.
Reprod Sci 2009 Nov;16[11]:1034-9.

20

Exceptions during Pregnancy

- AGCs or AIS
  - » ECC and endometrial biospy are **unacceptable** during pregnancy based on ASCCP guidelines
  - » The follow up of these patients is per ASCCP guidelines

21

21

Excisional Biopsy in Pregnancy

- Risk of progression from CIN 2-3 to microinvasive/invasive cancer is low
  - » 30% at 30 years
- Rate of spontaneous regression postpartum is high
  - » 34-70%
- Rate of incomplete excision is high

Therefore, colposcopy each trimester with re-evaluation with cytology, colposcopy, etc NO sooner than 6 weeks postpartum

Lancet Oncol 2008 May;9[5]:425-34

22

22

LEEP and CKC

- LEEP
  - » Increases risk of preterm birth, low birthweight infants and C/S.
    - RR 1.6
  - » Associated with complications when performed during a pregnancy
    - Associated with heavy bleeding in 5-15% of patients when performed during pregnancy
    - Up to a 25% risk of spontaneous abortion
    - 50% of women will have persistent cervical dysplasia (due to incomplete excision)
  - » Can be done when invasive cancer cannot be excluded
  - » Consider hemostatic cerclage

23

23

"Coin" Biopsy

- "Coin" Biopsy-not as deep as a typical "cone" and should be done ONLY in the case of diagnosing invasion and NOT intended to remove the entire transformation zone
- Consider hemostatic cerclage

24

24

Natural History of CIN in Pregnancy

- Does NOT warrant interruption of the pregnancy
- Local inflammatory reaction due to cervical trauma may improve regression rates
  - NSVD 67%
  - C/S 13%
- Base delivery on obstetrical indications
- Consider colposcopy 6 weeks post-partum

25

25

Case

- 33 y.o. G6P4A1 referred with new diagnosis of IB cervical cancer. LMP uncertain, however + pregnancy test at referring OB/Gyn office
- PmHx: non-contributory
- PGynHx: no abnormal pap, last 3 years ago
- Social Hx: married, monogamous, non-smoker

26

26

Case Continued

- Physical exam:
- 2 cm exophytic cervical lesion, negative parametria on exam
- U/S for dates as uncertain LMP consistent with 10 wk IUP
- Cervical Bx: SCCa Cervix
- Extensive counseling…patient declined radical hysterectomy or radiation with fetus in situ. Opted for detailed U/S and cisplatin chemotherapy beginning in second trimester with elective C/S radical hysterectomy

27

27

Signs and Symptoms of Cervical Cancer in Pregnancy

- IA-no symptoms
- IB-
  - » 59% vaginal bleeding/spotting
  - » 29% vaginal discharge
  - » 63% abnormal pap smear
- Advanced stages (II-IV)
  - » Pelvic/flank pain
  - » Sciatic
  - » Chronic anemia
  - » Obstructive sx (urinary, GI)

28

28

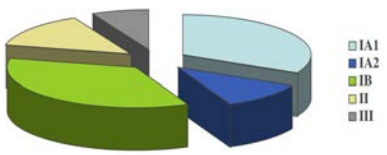
Treatment

- Assessment of the extent of the cancer
  - » MRI may be helpful
- Accurate appraisal of gestational age
- Thorough ultrasound examination of the fetus for anomalies
- Screen for serum markers of aneuploidy and spinal cord abnormalities
- Multidisciplinary meeting with gyn oncology, MFM, neonatology, social work, radiation oncology
- Need to be VERY sensitive to religious, ethical, moral and cultural issues

29

29

Stage at the Time of Diagnosis



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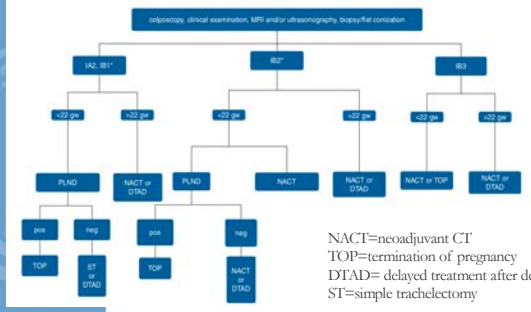
Cervical Cancer During Pregnancy



NACT=neoadjuvant CT
TOP=termination of pregnancy
DTAD= delayed treatment after delivery
ST=simple trachelectomy

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31

Chemoradiation for Cervical Cancer in Early Pregnancy

- Radiation in early pregnancy associated with rapid abortion
- Some authors recommend routine hysterotomy prior to starting radiation- this is debatable
  - » Decrease psychological impact
  - » Decreased obstetrical related complications such as uterine rupture, DIC, bleeding, etc

32

32

Chemoradiation for Cervical Cancer in Pregnancy Diagnosis in 3rd trimester

- Significant gains in fetal outcome can be made between 28-32 weeks
- 4 week delays are not felt to impact mother's prognosis
- Should not delay therapy beyond 32-34 weeks

33

33

Delayed Treatment After Delivery

- Close tumor surveillance is recommended
  - » Regular pelvic exams
  - » Visual inspection of the tumor
  - » Colposcopy in cases of microscopic disease
- Some advocate serial MRI assessment
- Obstetrical care as indicated
- Delay delivery until 37 weeks if possible
- C-section with simple or radical hysterectomy +/- SLN or LAD for early stage disease
- C-section and radiation for advanced disease
  - » Stay out of the LUS
- If disease completely excised during pregnancy, no oncologic indication for C-section

34

34

Case continued

- Patient opted for chemotherapy starting at 14 weeks
- Cisplatin 75 mg/m2 every 3 weeks
- Detailed scan with MFM and genetics consultation
- Pelvic exam every 3 weeks (with chemotherapy cycle)
- After 2 cycles of chemotherapy lesion completely regressed
- C/S with radical hysterectomy at 34 weeks
- No residual tumor
- NED at >7 years, daughter in 2nd grade

35

35

Obstetrical Care and Issues

- Need accurate gestational age assessment
- Assess structural development of the fetus
- Preference is carboplatin over cisplatin due to ototoxicity
- Platinum drugs are associated with small for gestational age infants
  - » Serial U/S to assess growth, AF, Cervical length
- C-Section if persistent disease, can consider vaginal delivery if cancer fully excised
- VTE
- Delay breast feeding for 3 weeks from last chemotherapy
- Examine placental for metastatic disease-VERY rare to metastasize to fetus
  - » 0.1% (melanoma, breast, leukemia, lymphoma)

J Clin Oncol 2003;21:2179

36

Mode of Delivery

- Sood, et al (n=56)
  - 14% RR in C/S deliveries
  - 56% RR in NSVD deliveries
  - In advanced disease, recommend XRT in 1st or 2nd trimester without hysterotomy
- Cliby, et al reported on 4 RR in episiotomy site, 3 patients died
  - Data suggest that these infants should be delivered via C/S

Obstet Gynecol Clin North Am. 1998 Jun;25(2):343-52
Obstet Gynecol. 1994 Aug;84(2):179-82

37

37

Delay of Definitive Treatment of Cervical Cancer in Pregnancy

Year	Stage	# patients	Delays (weeks)	Outcomes
1992	I	8	10-16	All alive (40 m)
1993	IA-IB	8	8-30	All alive (23 m)
1995	IB1	2	18-19	All alive (66 m)
1995	IB	7	3-40	All alive (37 m)
1996	IA1-IB1	11	3-32	All alive (118 m)
1998	IB-IIA	6	2-10	1 rec/1 death (82 m)
1998	IB-IIA	2	11-29	1 rec (14 m)
2002	IA1	8	9-25	All alive (120 m)
	IA2-IIA	5	6-13	All alive (103 m)

38

38

Ovarian Masses in pregnancy

39

39

- Ovarian masses occur in 1:80 to 1:2,500 pregnancies with at most 2-5% being malignant
- LMPs constitute 27-35% of ovarian "malignancies" dx during pregnancy
- Epithelial malignancies form 23-30% of all cases of ovarian cancers associated with pregnancy
- In Caucasians, dysgerminoma is the single most frequent malignant tumor dx during pregnancy.
- Typical tumor markers associated with "false" positives during pregnancy

40

Pathology

- Ovarian cancers in pregnancy are often non-epithelial
  - » 45% germ cell tumors
    - ~ 1/3 dysgerminomas
    - ~ 1/3 endodermal sinus tumors
    - ~ 1/3 immature teratomas
  - » 38% epithelial tumors
  - » 10% sex cord-stromal tumors
  - » 7% miscellaneous
- *"Ovarian cancer" in pregnancy may also be metastases*

41

41

Case

- 38 yo G2 P1 at 13 weeks gestation presents with a LLQ mass.
- Pt reports that the mass has been there for almost 1 year and gets larger when she needs to move her bowels
- Denies pain, pressure, GU symptoms

42

42

Case

- No significant PMH or PSH
- Exam
  - » Uterus is soft and gravid, 13-14 weeks' size. No palpable adnexal masses or cul-de-sac nodularity. The mass in the left lower quadrant did not seem to extend into the pelvis
- MRI
  - » 6cm "solid" mass in the L iliac fossa that is intimately associated with the sigmoid colon
- U/S guided Bx
  - » Papillary serous carcinoma with psammoma bodies

43

43

Diagnosis/Presentation

- Most patients are asymptomatic
  - » Adnexal masses found on "routine" obstetrical ultrasound
  - » Increasing incidence of adnexal masses in pregnancy due to increased use of routine ultrasound: 2-10%
  - » Recent series show 50%-70% of patients present asymptomatically
- Mass found at time of c-section
  - » 8%-24% found at surgery

Perinatology 2010; 2:13-21

44

44

Diagnosis/Presentation

- Pain/Torsion
  - » 13%-25% present with symptoms of pain related to torsion and/or rupture
  - » Higher risk of torsion in pregnancy because of more ovarian mobility and longer vascular pedicle

45

45

Evaluation of adnexal mass

- Ultrasound
  - » Often both diagnosis and first step in evaluation
  - » Should be first radiologic study obtained in patients presenting with pain or mass on exam
  - » Easy and safe
- Sonographic appearance
  - » Simple or multi-cystic masses more likely to resolve spontaneously (83-95% vs. 40%)
  - » Size matters (n=18,391)
    - Masses less than 5-6 cm are rarely malignant and often resolve
    - Masses >6 cm rarely resolve spontaneously

Obstetrics and Gynecology, vol. 105, no. 5, part 1, pp. 1098–1103, 2005
American Journal of Obstetrics and Gynecology, vol. 181, no. 1, pp. 19–24, 1999

46

Evaluation of adnexal mass

- Sonographic appearance
  - » Ascites
    - Raises suspicion for malignancy
    - Portends a higher stage and poorer prognosis
    - Combining two recent series revealed 11/44 patients presented with early ascites on U/S
      - » 8/11 had stage III or IV disease
      - » All 8 eventually died of their disease

47

47

Evaluation of adnexal mass

- MRI
  - » Similar to ultrasound in ability to evaluate the character of masses (complexity, etc)
  - » Expensive
- CT
  - » Ionizing radiation
    - 1-3 rads per CT of abdomen/pelvis
  - » May be better for looking at peritoneum and bowel

48

48

Management

Expectant management
- Simple cysts under 5 – 6 cm
- Asymptomatic simple cysts >6 cm
  - Probably benign but consider cystectomy because of torsion risk
- Smaller multicystic masses that do not change in size on serial radiologic exams

Surgical evaluation
- Complex masses over 6 cm
- Persistent symptomatic simple cysts
- Masses that are enlarging on serial exam

49

49

Table 2: Clinical presentation and frequency of spontaneous resolution of adnexal masses in pregnancy [3, 4, 9–11, 18–20].

	N	Asymptomatic	Symptomatic	Spontaneous resolution
Bernhard et al., 1999 [9] (>5 cm/complex)	102	78.4%	21.6% (pain or palpable mass)	68.6%
Zanetta et al., 2003 [18]	79	86.1%	13.9% (pain)	51%
Agarwal et al., 2003 [19]	14	35.6%	50% (pain or discomfort) 14.2% (larger than expected uterus)	NA
Condous et al., 2004 [20]	161	43.7%	56.3% (pain or genital bleeding)	71.7%
Schmeler et al., 2005 [10] (>5 cm)	59	92%	8% (pain)	1,7%
Kumari et al., 2006 [11]	20	50%	35% (pain) 15% (NE)	NA
Balci et al., 2008 [3]	36	30.6%	69,4% (pain)	NA
Aggarwal and Kehoe, 2011 [4] (review)[Ⓒ]	809	65.4%	16.8% (pain) 9% (bleeding/dystocia/rupture)	30.7%

http://dx.doi.org/10.1155/2016/3012802

50

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http://dx.doi.org/10.1155/2016/3012802

51

Management

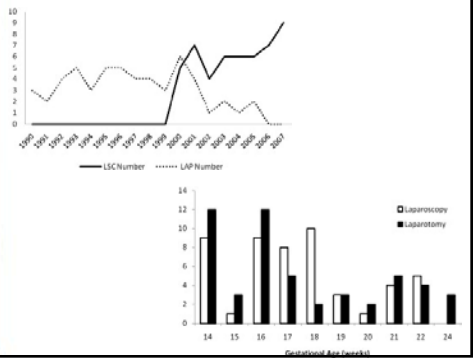
- Surgery
  - » Laparoscopy is a reasonable alternative to laparotomy
  - » Ideally in the mid second trimester
    - Lowest morbidity to mother and fetus
  - » Risks of surgery
    - Miscarriage
    - PPROM
    - Pre-term labor
    - Intra-uterine demise
  - » More morbidity associated with emergent surgeries

52

52

Surgery in Pregnancy

- IF possible postpone until 2nd trimester



53

Management

- Surgery
  - » For unilateral mass, cystectomy, salpingo-oophorectomy, oophorectomy
  - » Obtain a frozen section
    - If positive for carcinoma, appropriate staging biopsies and lymphadenectomy should be performed if possible based on uterine size
  - » Do not need to remove contralateral ovary unless grossly involved

54

54

Management

- Germ cell tumors
  - » Dysgerminomas
    - Most common
    - Often early stage (80+%)
    - Usually a solid unilateral mass
    - 10-15% bilateral
    - Surgical debulking/staging
      - » USO with omentectomy, washings, biopsies and ipsilateral node dissection
      - » Do not need to biopsy contralateral ovary if it is grossly normal
    - Fertility sparing surgery acceptable

55

55

Management

- Germ cell tumors
  - » Dysgerminoma
    - If early stage (IA or IB) then do not need adjuvant therapy
    - If advanced stage, there are reports of giving etoposide and cisplatin with delivery of healthy infants
    - Can monitor LDH
      - » Should be normal in the absence of pre-eclampsia

56

56

Management

- Germ cell tumors
  - » Endodermal sinus tumors
    - Second most common germ cell tumor
    - Extremely rare in pregnancy
    - Surgical approach same as for dysgerminoma
    - Will often need adjuvant chemotherapy
      - » 5-year survival with surgery alone is 13%
      - » With chemo long-term survival of early stage disease is 80%
    - Chemotherapy
      - » Bleomycin, etoposide, cisplatin (BEP)

57

57

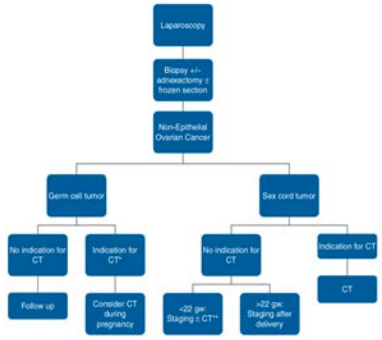
Management

- Sex cord-stromal tumors
  - Granulosa cell, fibromas, thecomas, sertoli-leydig
  - Extremely rare in pregnancy
  - May present with virilization
  - Most are Stage I at presentation
  - Surgical resection alone is usually adequate
  - Advanced disease can be treated with adjuvant BEP

62

58

Management of nonepithelial ovarian cancer in pregnancy



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59

Management

- Epithelial ovarian cancer
  - Rare in pregnancy compared to germ cell tumors
  - Serous are the most common (75%)
  - Often patients present with vague complaints
  - Often bilateral (65% of serous tumors)
  - Surgery
    - Complete staging usually not possible unless patient willing to terminate pregnancy
    - USO with omentectomy, biopsies and lymphadenectomy acceptable

60

60

Management

- Epithelial ovarian cancer
  - » Early stage
    - If IA, then close monitoring with consideration for completion hysterectomy with USO after delivery
  - » Advanced disease (IC - IV)
    - Patients will need adjuvant chemotherapy
  - » Chemotherapy
    - Single agent cisplatin/carboplatin during pregnancy
    - Add paclitaxel after delivery
      - » More recently believed to be okay during pregnancy
  - » Strong consideration for completion hyst and staging after delivery

61

61

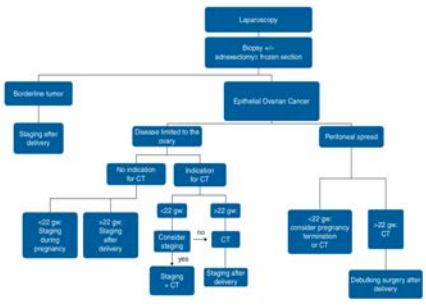
Management

- Epithelial ovarian cancer
  - » CA-125
    - Normally elevated in the first and early second trimester of pregnancy
    - Should only be used to follow those with confirmed disease, not as a screening test
  - » Borderline (low malignant potential) tumors
    - Surgery alone is adequate

62

62

Management of epithelial ovarian cancer in pregnancy



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63

Prognosis

- For all tumor histologies, pregnancy does not appear to negatively impact of survival

64

64

Case con't

- At 14 wks pt underwent Exlap/RSO/resection of left pelvic mass and adjacent descending colon/ omentectomy/L paraaotic LND
- Path consistent with Stage IIIC grade 1 serous primary peritoneal carcinoma
- Pt received 5 cycles single agent carboplatin
- CA 125 59.8 pre-op, decreased to 32 at delivery and was 13 after delivery

65

65

Chemotherapy during pregnancy

- Typically postpone until after 20 weeks
- Carboplatin and paclitaxel can be considered the standard of care in the gravid female
- Data is limited to case reports
- 37 women treated with platinum based chemotherapy during pregnancy
  - » All infants born alive
    - One with transient anemia and resp. distress
    - One with ventriculomegally and cerebral atrophy (BEP)
    - One with alopecia, hearing loss and hematological abnormalities (E)

66

Neonatal considerations

- Evaluate placenta
- Evaluate neonatal labs
- If cddp given, hearing tests during infancy
- If anthracyclines, echocardiogram and long term follow up (every 3 years)
- Neurocognitive evaluation for development every 3 years
- Psychosocial support particularly if mother not expected to survive longer term.

67

Conclusions

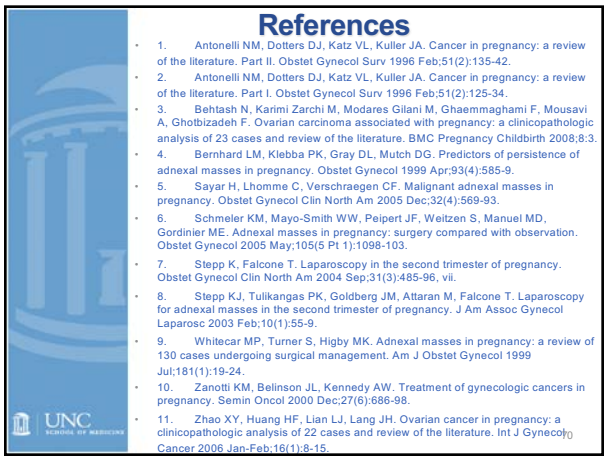
- Gynecologic malignancies in pregnancy are rare
  - » Treatment is based on time diagnosis is made, stage and extent of disease
- Cervical cancer: treatment delay to complete pregnancy does not appear to adversely effect outcomes
- Adnexal masses in pregnancy are not uncommon but are rarely malignant
  - » Sonographic appearance can guide management
- Staging important for both prognosis and to guide the possible need for adjuvant chemotherapy during gestation (ovarian cancer)
  - » Chemotherapy can be safely given during pregnancy
  - » Pregnancy does not appear to adversely effect the outcome

68

Conclusions

- Treatment should mimic that in the non-pregnant patient as much as possible
- Interdisciplinary team is essential, need to consider ethical and religious issues
- Exam the placenta histologically as the fetal mortality is about 25% for all placental metastases
- Data is often limited to case reports
  - » Bias as only publish “positive” results
  - » Definition of pregnancy “associated”. Is it those dx during pregnancy or those 9 months prior or 1 year post?

69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70

70