Breast Cancer During Pregnancy

Introduction

- Breast cancer during pregnancy (BCP) vs pregnancy associated breast cancer (PABC)
  - Includes lactation period/1 year postpartum
- Most common invasive cancer in pregnancy
  - Incidence estimate 6.5/100.000 live births
- Increased risk age >35
  - Incidence expected to rise with more women delaying child bearing

Abenhaim et al, Breast J 2012
Loibl, JAMA Oncol 2015

Presentation

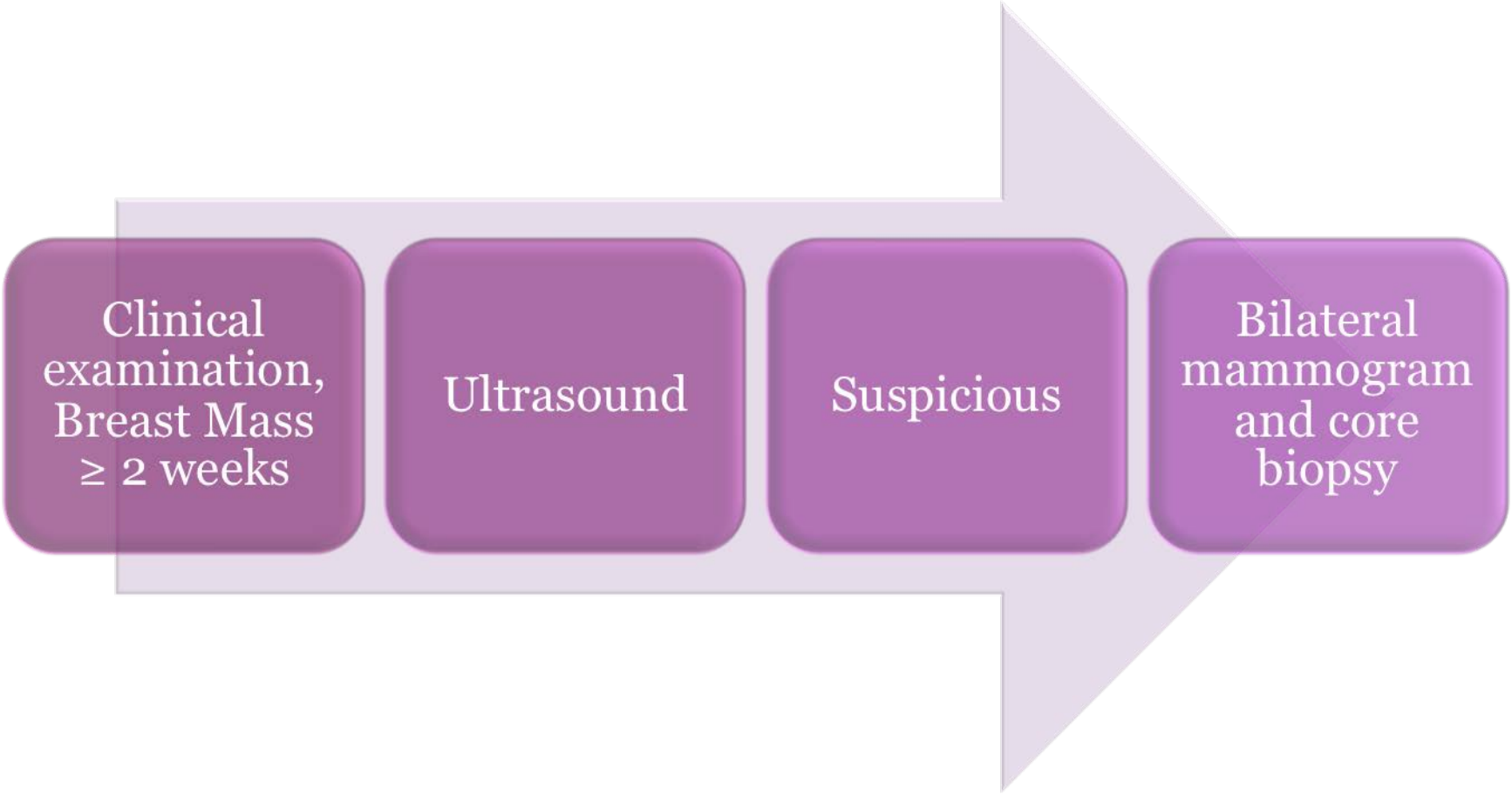
- Young non-screened population
- Palpable mass
- High index of suspicion among health care providers needed

- Delay in diagnosis common
  - Patient profile not typical
  - Physiologic changes in breast
  - Most breast lumps in pregnancy are benign
  - No specific risk factors known
  - Bidirectional effect of pregnancy

Early Detection

- Thorough breast examination at first antenatal visit
  - Consider US in high-risk women
- Counsel women on breast self-awareness
- Encourage to seek help if changes noticed
- High index of suspicion among health care providers
  - Breast mass should prompt urgent evaluation

Diagnosis – Triple Assessment



Imaging

- Sensitivity of breast imaging similar to that in non-pregnant women
- Ultrasound recommended for initial evaluation:
  - Characterization of mass
  - Lymph node basins
  - Tumour response to neoadjuvant therapy

Yang et al, Radiology 2006
Loibl et al, Cancer 2006

Imaging

- Mammogram indicated when breast cancer suspected
  - Complementary to ultrasound
  - Characterizes mass, microcalcifications, breast density
  - Safe with abdominal shielding, fetal radiation 0.4 mrad
- MRI insufficient data on safety of gadolinium

Yang et al, Radiology 2006
Loibl et al, Cancer 2006

Pathology

- Pathologist should be informed about pregnancy
  - FNA often overdiagnosis due to proliferative state
- Core biopsy preferred
  - Grading
  - Hormone receptor status
  - HER2 analysis
  - E-cadherin
  - Ki67
  - Lymphovascular invasion
- Predominantly invasive ductal carcinoma
- Compared to non-pregnant women:
  - Advanced stage
    - Larger tumours
    - Lymph node involvement
    - Distant metastases
  - Lymphovascular invasion
  - Hormone receptor negative

Litton et al, Oncologist 2010
Middleton et al, Cancer 2003
Loibl et al, Cancer 2006

Pathology

- Similar to age-matched non-pregnant breast cancers
- Age at diagnosis rather than pregnancy determines biologic behaviour

Middleton et al, Cancer 2003
Loibl et al, Cancer 2006

Staging

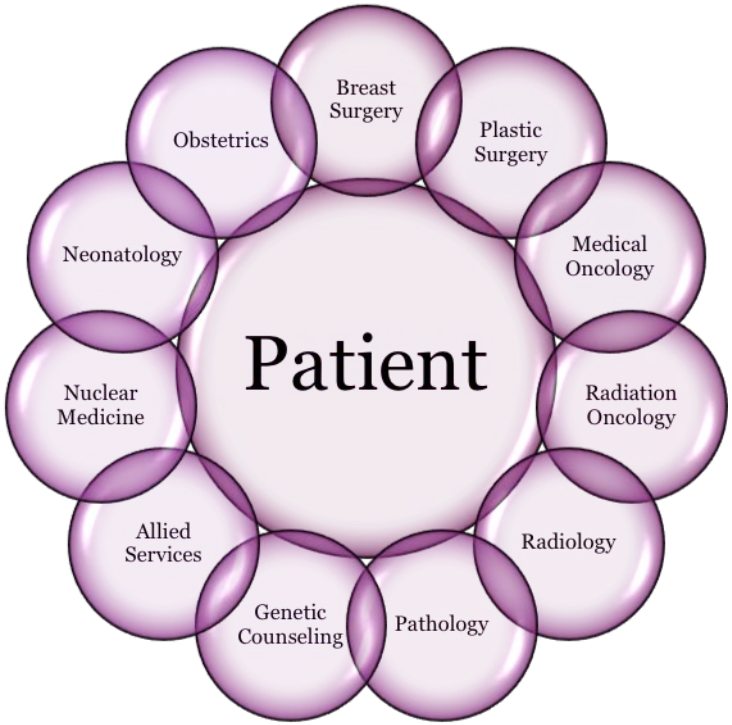
- Baseline obstetric evaluation before staging investigations and treatment
- Studies tailored to minimize radiation exposure to fetus
  - Chest xray, liver ultrasound, baseline bloods
  - Non-contrast skeletal MRI
  - CT and bone scans not recommended
  - Consider echocardiogram especially if AC planned

Management

- Follows standards in non-pregnant women as closely as possible
- Few data available
  - Large RCTs impossible
  - International registries and cohort studies offer best guidance
- Individualized approach
  - Gestational age at diagnosis
  - Stage of disease
  - Tumour biology
  - Patient preferences

Management

- Multidisciplinary team mandatory
- Special consideration to
  - Obstetrician
  - Neonatologist
  - BRCA testing
  - Psychological support



Termination of Pregnancy

- Does not improve outcome
- Personal decision

Cardonick et al, Cancer J 2010

Surgery

- Can be performed safely throughout pregnancy
  - No higher rate of spontaneous loss in 1st trimester
- Mastectomy and BCS options
  - Radiation delayed to postpartum period
- Reconstruction
  - Immediate reconstruction with tissue expanders
  - Tissue based reconstruction delayed to postpartum period

NCCN guidelines
Cardonick et al, Cancer J 2010
Amant et al, Lancet 2012
Lohsiriwat et al, Breast 2013

Surgery - Axilla

- SLNB
  - Dye unknown potential for teratogenicity, allergic reactions
  - Radiocolloid maximum exposure to fetus 0.43 rad
  - 1-day protocol

- Most recent cohorts suggests SLNB to be safe and accurate during pregnancy
- Decisions should be individualized
  - Discussion with patient and MDT

Keleher et al, Breast J 2004
Mondi et al, Ann Surg Oncol. 2007
Gropper et al, Ann Surg Oncol 2014
Toesca et al, Gynecol Surg 2014

Chemotherapy

- Indicated in most cases
- Risk of abortion and congenital malformations increased in 1st trimester

- 2nd and 3rd trimester
  - Fetal malformation rate 3.8%
  - Neoadjuvant or adjuvant
  - Anthracycline-based regimens most common
  - Taxanes, platinums and dose-dense schedules limited data but seem safe options

Hahn et al, Cancer 2006
Cardonick et al, Cancer J 2010
Mir et al, Ann Oncol 2010
Loibl et al, JAMA Oncol 2015

Chemotherapy

- Prenatal care with regular growth scans
- No chemotherapy after 35 weeks or within 3 weeks of planned delivery
- Can be commenced immediately after vaginal delivery and 1 week after C/S
- Breastfeeding contraindicated during chemotherapy

Targeted Therapy

- Tamoxifen
  - Deferred to postpartum period
  - Associated with birth defects
- Trastuzumab
  - HER2 expressed in fetal renal epithelium
    - Oligo-/anhydramnios, renal failure and fetal death
  - Deferred to postpartum period

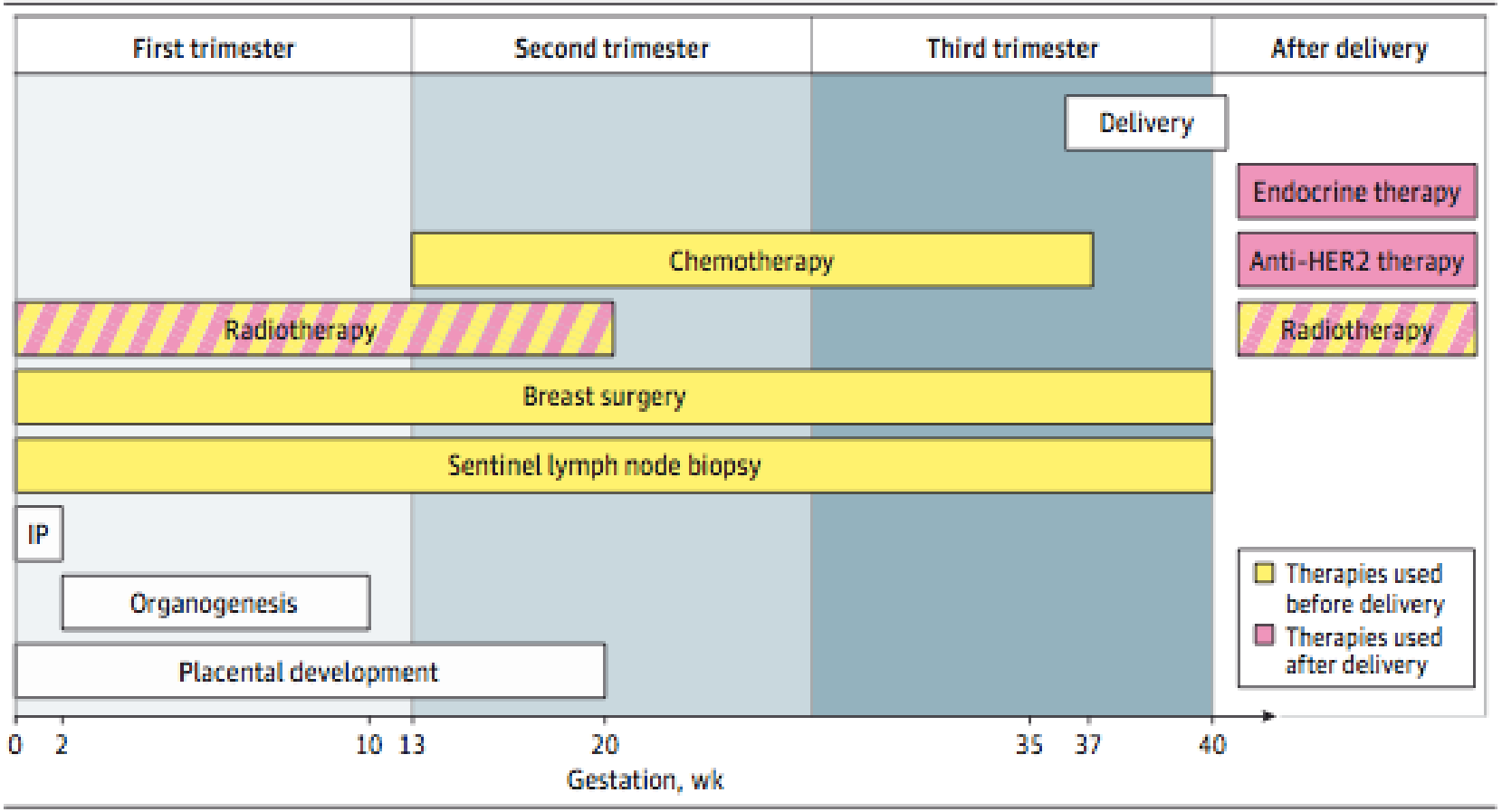
Zagouri et al, Breast Cancer Res Treat 2013
Isaacs et al, Gynecol Oncol 2001
Amant et al, Lancet 2012

Radiation Therapy

- Generally delayed to postpartum period
  - Associated fetal exposure risks
- May be considered in 1st and early 2nd trimester
  - In appropriately counseled women
  - Fetal doses below the threshold of 5 rad
- Breastfeeding is contraindicated during radiation therapy

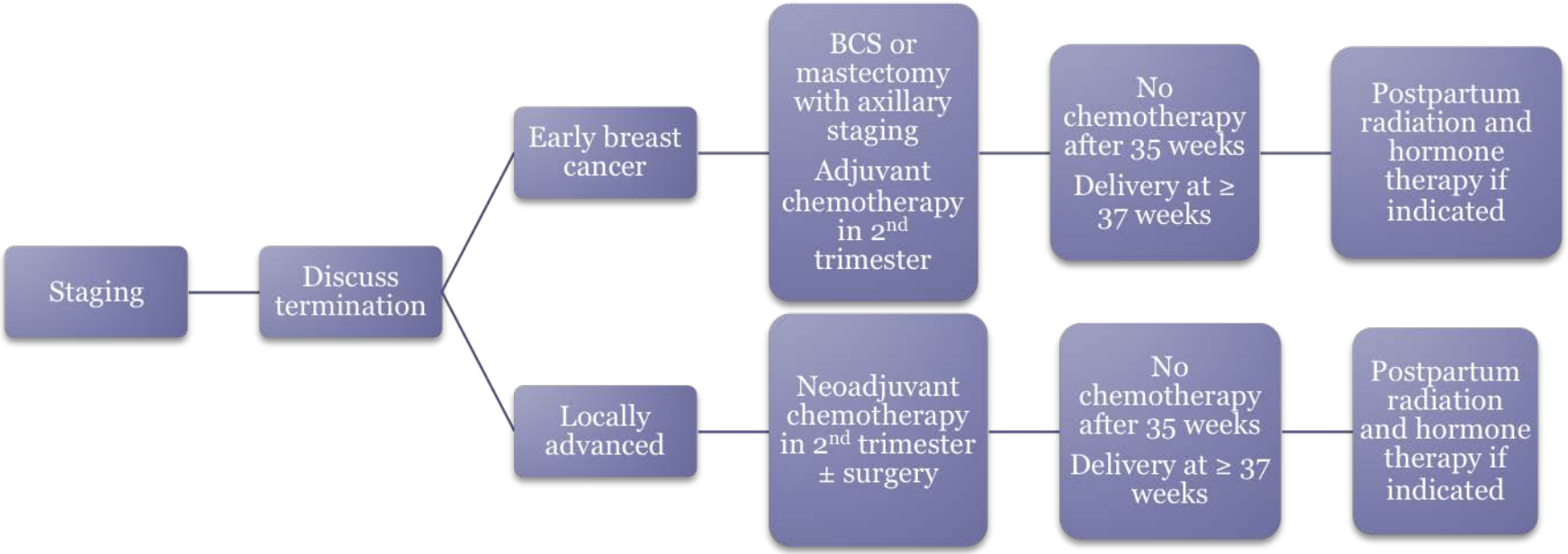
Martin, Clin Obstet Gynecol 2011
Amant et al, Lancet 2012
Loibl et al, JAMA Oncol 2015

Therapeutic Options

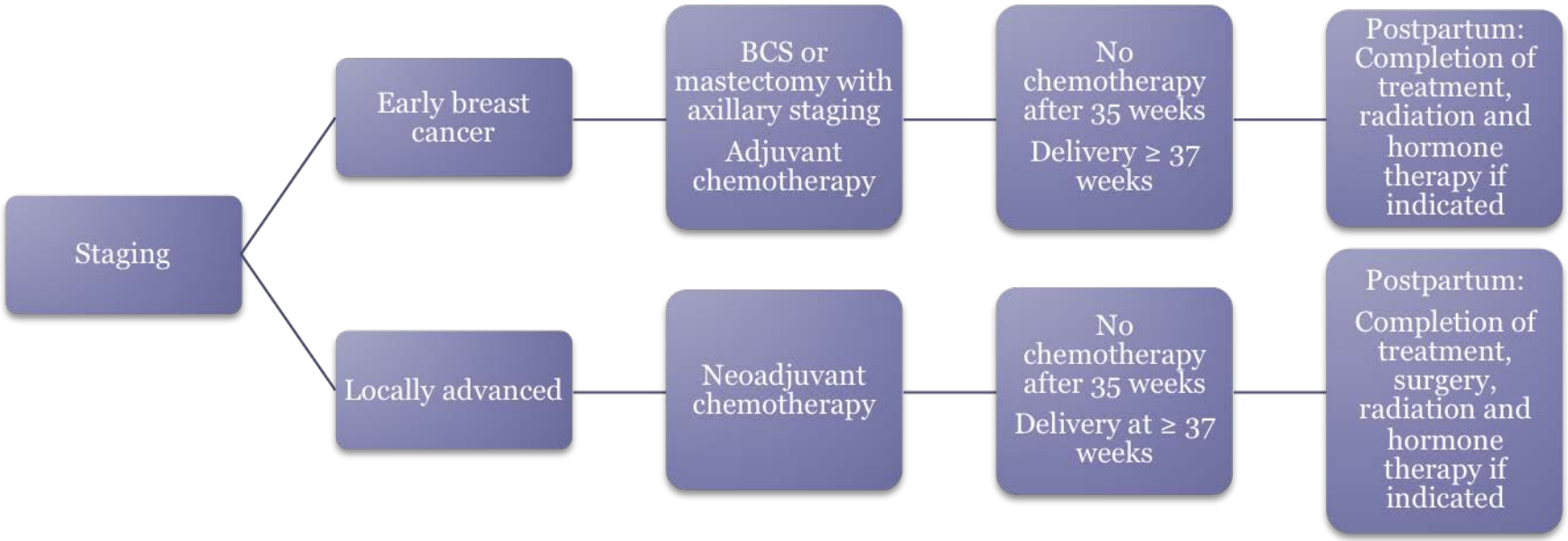


Loibl et al, JAMA Oncol 2015

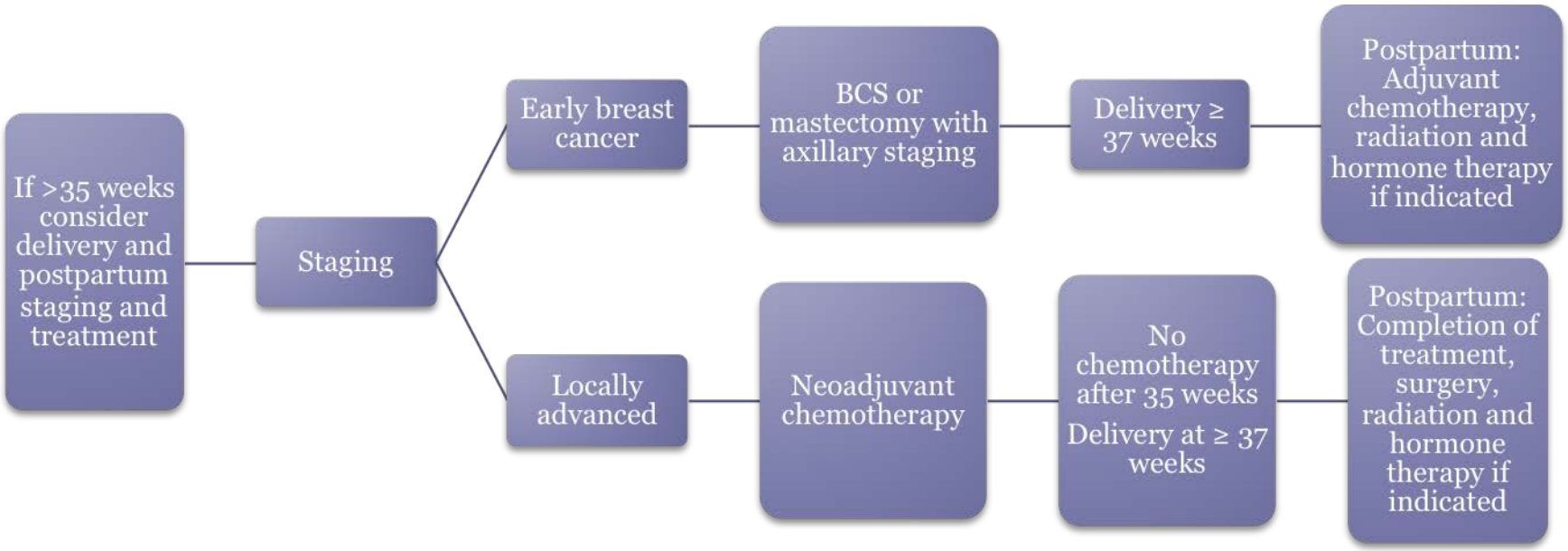
Sequence 1st Trimester



Sequence 2nd or Early 3rd Trimester



Sequence Late 3rd Trimester



Prognosis

- Conflicting results in literature
- Poorer prognosis may relate to
  - Advanced stage at presentation
  - Possible treatment delays/omissions over concerns of fetal outcome
  - ? Direct pregnancy-related effects
    - Elevated hormone levels increase biologic aggressiveness of cancer cells
    - Hormonal changes increase vascularization/inflammatory cell recruitment

Rodriguez et al, Obstet Gynecol 2008
Beadle et al, Cancer 2009
Amant et al, J Clin Oncology 2013

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

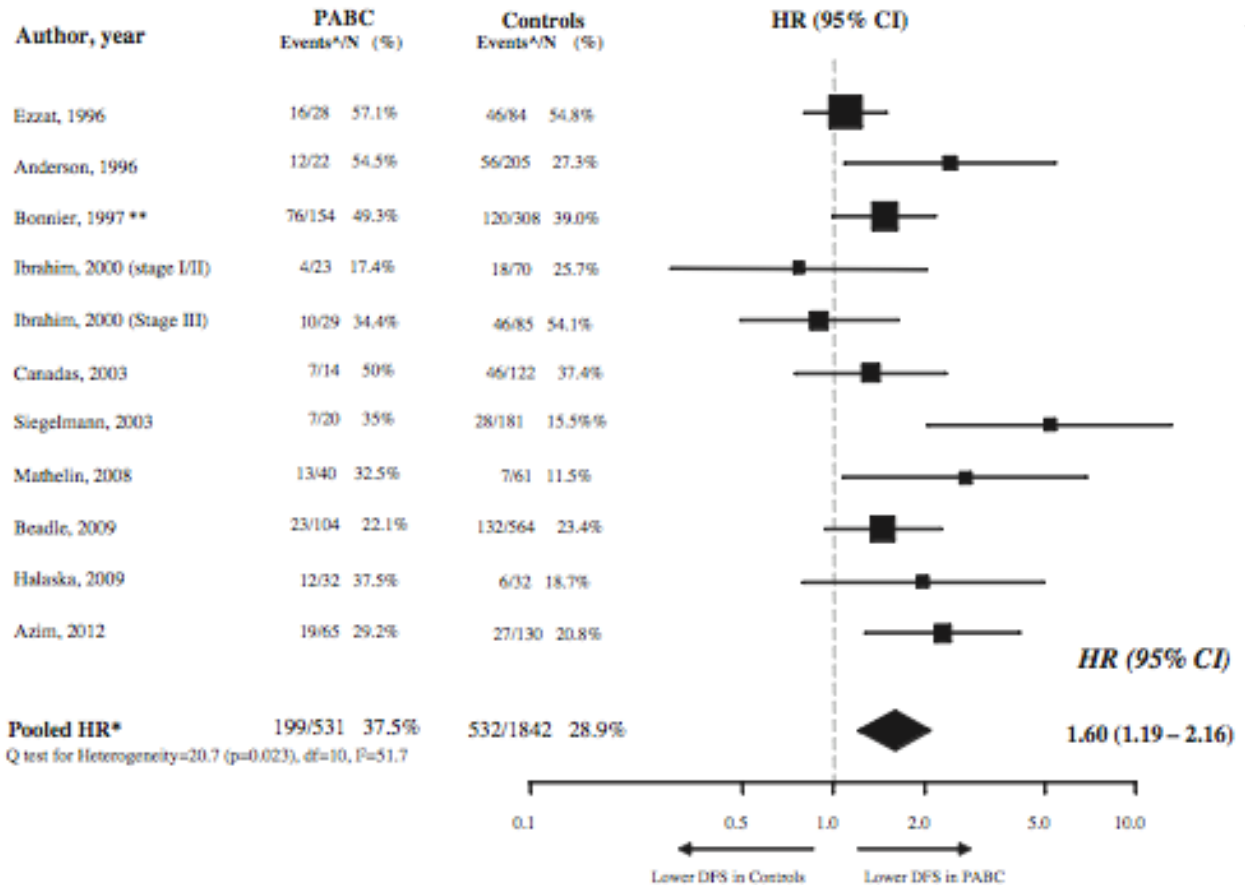
Controversy

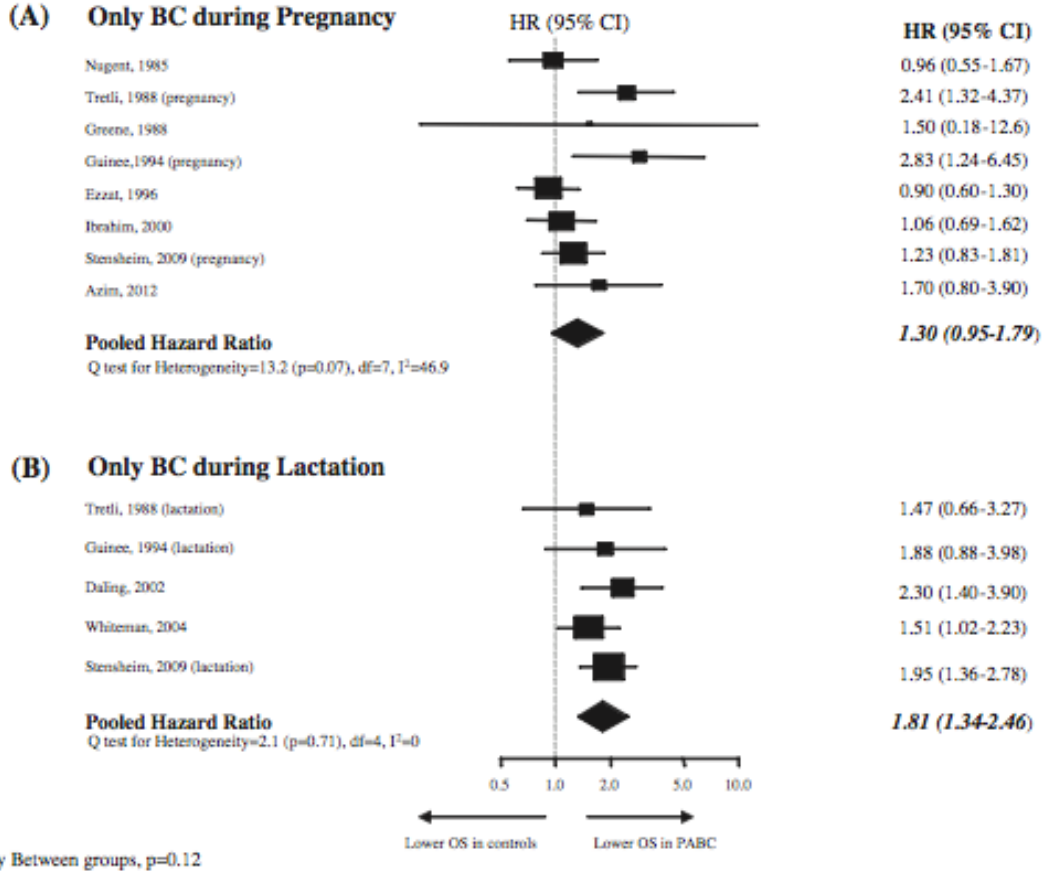
Prognosis of pregnancy-associated breast cancer: A meta-analysis of 30 studies

Hatem A. Azim Jr. [a,*], Luigi Santoro [b], William Russell-Edu [c], George Pentheroudakis [d], Nicholas Pavlidis [d], Fedro A. Peccatori [e]

[a] Breast Cancer Translational Research Laboratory (BCTL) J.C. Heuson, Université Libre de Bruxelles, Institut Jules Bordet, 1000 Brussels, Belgium
[b] Department of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
[c] Library, European Institute of Oncology, Milan, Italy
[d] Department of Medical Oncology, University of Ioannina, Ioannina, Greece
[e] Department of Medicine, Fertility and Procreation Unit in Oncology, European Institute of Oncology, Milan, Italy

- PABC independently associated with poor survival
- Particularly those diagnosed post-partum


Author, year
PABC
Events^/N (%)
Controls
Events^/N (%)
HR (95% CI)
Ezzat, 1996 16/28 57.1% 46/84 54.8%
Anderson, 1996 12/22 54.5% 56/205 27.3%
Bonnier, 1997 ** 76/154 49.3% 120/308 39.0%
Ibrahim, 2000 (stage I/II) 4/23 17.4% 18/70 25.7%
Ibrahim, 2000 (Stage III) 10/29 34.4% 46/85 54.1%
Canadas, 2003 7/14 50% 46/122 37.4%
Siegelmann, 2003 7/20 35% 28/181 15.5%%
Mathelin, 2008 13/40 32.5% 7/61 11.5%
Beadle, 2009 23/104 22.1% 132/564 23.4%
Halaska, 2009 12/32 37.5% 6/32 18.7%
Azim, 2012 19/65 29.2% 27/130 20.8%
HR (95% CI)
Pooled HR* 199/531 37.5% 532/1842 28.9% 1.60 (1.19 – 2.16)
Q test for Heterogeneity=20.7 (p=0.023), df=10, I²=51.7
0.1
0.5
1.0
2.0
5.0
10.0
Lower DFS in Controls
Lower DFS in PABC



ity Between groups, p=0.12

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognosis of Women With Primary Breast Cancer Diagnosed During Pregnancy: Results From an International Collaborative Study

Frédéric Amant, Gunter von Minckwitz, Sileny N. Han, Marijke Bontenbal, Alistair E. Ring, Jerzy Giermek, Hans Wildiers, Tanja Fehm, Sabine C. Linn, Bettina Schlehe, Patrick Neven, Pieter J. Westenend, Volkmar Müller, Kristel Van Calsteren, Brigitte Rack, Valentina Nekljudova, Nadia Harbeck, Michael Untch, Petronella O. Witteveen, Kathrin Schwedler, Christoph Thomssen, Ben Van Calster, and Sibylle Loibl

- Only included BCP, N=447
- Median follow-up 61 months
- Similar OS when compared to non-pregnant patients

Breast Cancer Res Treat (2013) 138:549–559
DOI 10.1007/s10549-013-2437-x

EPIDEMIOLOGY

Postpartum diagnosis demonstrates a high risk for metastasis and merits an expanded definition of pregnancy-associated breast cancer

Eryn B. Callihan · Dexiang Gao · Sonali Jindal · Traci R. Lyons · Elizabeth Manthey · Susan Edgerton · Alexander Urquhart · Pepper Schedin · Virginia F. Borges

- Patients diagnosed within five-years postpartum compared to nulliparous age-matched control
  - Higher 5-year distant recurrence rate (31.1 % vs 14.8%)
  - Lower 5-year overall survival (65.8 % vs 98%)
- Propose that the definition of PABC should include cases diagnosed up to 5 years post-partum

Prognosis

- Postlactation breast involution pro-oncogenic effect
- Worst outcomes in postpartum PABCs rather than during pregnany
- Age appears to be principal driver of increased mortality observed
- Pregnancy itself not proven to compromise prognosis

Rodriguez et al, Obstet Gynecol 2008
Beadle et al, Cancer 2009
Azim et al, Can Res Treat 2012

Conclusion

- Treatment possible during pregnancy
- Termination does not improve outcome
- Multidisciplinary management crucial
  - Tailor diagnostic strategy
  - Tailor treatment strategy


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