Cardiovascular Drugs -1
Hypertension

PHRM 203
Allison Beale
Overview

❤ Lecture one
  • Heart basics [www.texasheartinstitute.org/HIC/Anatomy/anatomy2.cfm](http://www.texasheartinstitute.org/HIC/Anatomy/anatomy2.cfm)
  • Hypertension

❤ Lecture two
  • Angina
  • Heart Failure
  • Anti-arrhythmics

❤ Lecture three
  • Anti-hyperlipidemics
  • Blood thinners and clotting agents
Heart Basics

♥ Heart Disease

- Coronary and Peripheral artery diseases
  - High BP (hypertension, HTN)
  - Angina - pain
  - Heart attack (myocardial infarction, MI) and Stroke - blockage leads to cardiac muscle or CNS death
  - Hyperlipidemia, etc.

- Heart Failure
  - Heart can not pump sufficient blood to maintain body functions
  - Congestive (CHF) - fluid fills pericardial sac and lungs

- Heart arrhythmias
  - Changes in heart beat
  - → heart disease, stroke, sudden cardiac arrest
Hypertension

-HTN = most common CV disease

- BP = systolic (contracting) / diastolic (filling)
- Normal BP = 115/75 (or ≤120/≤80 mmHg)
- Mild/Pre hypertension = 120-139/80-89
- Hypertension > 140/90; ↑risks
  - The 8th Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines hypertension as BP >140/90 OR on an antihypertensive medication.

- Prevalence varies - age, race, diet, gender
- ↑ incidence of renal failure, HF, stroke, CAD, PAD

- Usually asymptomatic until organ failure is imminent or has already occurred
Complications of HTN

- **Kidney failure**
  - 2nd most common cause after diabetes
- **Arteriosclerosis** (hardening of the arteries)
  - Atherosclerosis (plaque buildup in blood vessels)
- **Aortic aneurysms and dissections**
  - Thoracic
  - Abdominal
- **Heart failure** *(especially left side hypertrophy & failure)*
  - Coronary artery occlusion
    - Angina
  - Poor perfusion due to hypertrophy
- **Stroke**
- **Other end organ damage**
  - **Retinal damage** - Trouble with memory/learning
  - Epistaxis (nose bleed) - Metabolic syndrome
Defining HTN

• Measure BP using sphygomonanometer
  – No exercise, caffeine, smoking 1 hr before
  – Multiple measurements

• Blood pressure a continuum
  – ≥ 115/75 complications start
    • CV disease risk 2X each 20/10 rise
  – ≤140/90 goal for at risk patients
    • Chronic kidney failure
    • Diabetes
    • African Americans
  – Isolated systolic High BP (≥140/≤90)
    • “wide pulse pressure” in older adults 2-4X risk
Hypertension

❤️ “White coat” hi-BP versus true HTN

❤️ Life style modifications should be tried 1st and accompany any medication

- Dietary changes (e.g., DASH diet)
  - ↓ Na+, caffeine, alcohol; ↑K+, Ca++
- ↓ Weight
- ↑ Exercise
- ↓ Stress
- Quit smoking
# DASH Diet

*Dietary Approaches to Stop Hypertension*

<table>
<thead>
<tr>
<th>Type of food</th>
<th>Number of servings for 1600-2000 calorie diet</th>
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</thead>
<tbody>
<tr>
<td>Grains and grain products (include at least 3 whole grains per day)</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Fruits</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Vegetables</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Low Fat or Non Fat Dairy</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Lean meats (like chicken or fish)</td>
<td>1.5 - 2</td>
</tr>
<tr>
<td>Nuts, seeds and legumes</td>
<td>3 - 5 per week</td>
</tr>
<tr>
<td>Fats and sweets</td>
<td>2</td>
</tr>
</tbody>
</table>

Summary

General Treatment Strategy for Hypertension

1. Diagnosis- 3- 6 independent measurements of BP.
2. Determination of primary vs. secondary hypertension.
3. If secondary, treat underlying pathology.
4. If primary, initiate lifestyle changes
   - smoking cessation
   - weight loss
   - diet
   - stress reduction
   - less alcohol
   - etc.

CRITICAL POINTS!
- Goal- normalize pressure- decrease CO and/or TPR
- Strategy- alter volume, cardiac and/or VSM function

Used with permission from S. Bealer, Dept. Pharm./Tox., University of Utah
Hypertension

2nd-ary Hypertension - cause is known (5% of cases)

- Hyperthyroidism
  - TH ↑BP
- Oral contraceptives
  - Estrogen ↑renin-angiotensin system → ↑BP
- Pheochromocytoma
  - Catecholamine (NE, DA, Epi) secreting adrenal tumor → ↑HR, BP, [Glucose]blood
- Coarctation of aorta
  - Congenital narrowing of aorta → ↑BP in head and arms; ↓BP everywhere else; ↑↑work for heart
- Cushing’s disease
  - Pituitary adenoma → xs ACTH → xs cortisol from adrenals
- Primary Aldosteronism
  - 1/8 of hiBP cases, Conn’s syndrome = benign adrenal tumor
- Renal artery constriction
Hypertension

♥ Primary or *Essential* HTN - cause **unknown** (95% of cases)

- Risk factors:
  - Age
  - Hyperlipidemia - LDL >160 mg/dL (in normal person, this is high)
  - Diabetes and metabolic syndrome
  - Genetics (family history, sex, race)
  - Weight
  - Diet, including overuse of salt ($\geq 5.8$ gm/day) and types of fats
  - Smoking
  - Stress & stress management
  - Exercise (lack of)
  - Chronic inflammation (elevated "C reactive protein" levels)

- The **vast majority** of essential HTN patients have one thing in common:
  - **Arteriosclerosis** (hardening) of the arterioles
How the body regulates BP

- Nervous system
  - Medulla
  - Hypothalamus and Posterior Pituitary gland
- Vascular Autocoid Production
  - Endothelium
  - Mast cells
  - Platelets
- Kidney
- Adrenal gland
How the body regulates BP

1. Nervous system
   – Medulla (Ventral Surface of the Medulla, VSM)
     • Controls sympathetic and parasympathetic outflow (HR, conduction, contractility, vasoconstriction)
     • Baroreceptors in carotid arteries provide feedback
   – Hypothalamus and Posterior Pituitary gland
     • Antidiuretic hormone (vasopressin, ADH) → water retention and vasoconstriction (synthesis/release stimulated by AngII)
     • Adrenocorticotropic hormone (ACTH) → cortisol release

2. Vascular Autocoid Production

3. Kidney

4. Adrenal gland
   \text{ADH release triggered by: Hypotension (baroreceptors),} \ 
   \text{↑ osmolarity &/or ↑ ANG II (stimulate receptors on hypothalamus),} \ 
   \text{↑ sympathetic stimulation}
How the body regulates BP

1. Nervous system

2. Vascular Autocoid Production
   - Endothelium
     • Endothelin $\rightarrow$ vasoconstriction
     • NO, EDHF (endothelium-derived hyperpolarizing factor) $\rightarrow$ vasodilation
     • Prostacyclin (PGI$_2$) $\rightarrow$ vasodilation (antagonist to TXA$_2$)
   - Mast cells
     • Histamine $\rightarrow$ vasodilation
   - Platelets
     • Serotonin, ATP/ADP, Ca$^{++}$, Thromboxanes (TX’s) $\rightarrow$ vasoconstriction
   - Plasma proteins
     • Kinins $\rightarrow$ vasodilation (antagonist to AngII)

3. Kidney
4. Adrenal gland
How the body regulates BP

1. Nervous system
2. Vascular Autocoid Production
3. Kidney
   - Renin - Angiotensin II → vasoconstriction
     - Ang II → release of growth factors (e.g., vascular endothelial growth factor, VEGF)
       - ↑ # & size (proliferation and hypertrophy) of vascular smooth muscle cells
         » ↑ vascular tone → ↑BP
       - Fibrotic Δ’s (scaring) → ↑BP
     - Ang II → release of ADH & Aldosterone
     - Ang II → stimulates the sympathetic nervous system
4. Adrenal gland
How the body regulates BP

1. Nervous system
2. Vascular Autocoid Production
3. Kidney

4. Adrenal gland
   - Aldosterone → water retention in kidney → ↑ blood volume → ↑ BP
   - Cortisol → Sensitizes vascular smooth muscle to NE/EPI and acts as a diuretic → ↑ BP
   - Catecholamines → ↑ HR, contractility, conduction, vasoconstriction → ↑ BP
   - Progesterone is a potent inhibitor of the aldosterone receptor
     • Just before ovulation occurs, progesterone levels drop dramatically and an aldosterone rebound occurs contributing to PMS-related edema.
How the body regulates BP

- Nervous system
  - Medulla
    - Controls sympathetic and parasympathetic outflow (HR, Conduction, Contraction)
    - Baroreceptors in carotid arteries provide feedback
  - Hypothalamus and Posterior Pituitary gland
    - Antidiuretic hormone (vasopressin) → water retention and vasoconstriction
    - ACTH → cortisol release → ↑ BP

- Vascular Autocoid Production
  - Endothelium
    - Endothelin → vasoconstriction
    - NO, EDHF → vasodilation
    - Prostacyclin (PGI\textsubscript{2}) → vasodilation (antagonist to TXA\textsubscript{2})
  - Mast cells
    - Histamine → vasodilation
  - Platelets
    - Serotonin, ATP/ADP, Ca\textsuperscript{++}, Thromboxanes → vasoconstriction

- Kidney
  - Renin - Angiotensin II → vasoconstriction

- Adrenal gland
  - Aldosterone → water retention in kidney → ↑ blood volume → ↑ BP
  - Cortisol → Sensitizes vascular smooth muscle to NE/EPI, causes diuresis → ↑ BP
  - Catecholamines → ↑ HR, contractility, conduction, vasoconstriction → ↑ BP
Looking at some important mechanisms in the control of blood pressure

See handouts for key
“Taking medication for HTN”

• HTN = silent disease
  – You probably feel fine

• Lifetime commitment to taking meds
  – You won’t feel fine anymore

♡ Lots of causes, lots of meds in lots of classes

♡ Lots of errors: ADRs, Medicare, 2006
  ✃ Essential hypertension 28% of ADRs in 8.2M patients
  ✃ 2/3 of HTN patients on up to FIVE different drugs for HTN
Hypertension

“4” sites to pharmacologically regulate BP

1. Medulla (origin of sympathetic & parasympathetic outflow)
2. Blood Vessels
   - Resistance vessels (arterioles)
   - Capacitance blood vessels (venules)
3. Heart variables (pump output)
   - Rate = Chronotropy
   - Contractility = Inotropy
   - Conduction = Dromotropy
   - Relaxation = Lusitropy
4. Kidney variables (blood volume)
   - Water
   - Electrolytes
Classes of Antihypertensive Agents

1. Diuretics
2. Vasodilators
   - Calcium Channel Blockers
   - Other vasodilators
3. Anti-angiotensin II Drugs
   - ACE inhibitors, A2 receptor blockers or Direct Renin Inhibitors
4. β-Adrenergic Antagonists (β-Blockers)
5. Central Sympatholytics (α-2 agonists)
6. Peripheral α-1 Adrenergic Antagonists

CRITICAL POINTS!
1. Each designed for specific control system
2. Often used in combination
Antihypertensive Drugs

♥ Diuretics
• Thiazide-type
• Loop
• K⁺ sparing

♥ Sympatholytic drugs
• Peripheral α adrenergic antagonists
• CNS α₂ agonists ❧
• β Adrenergic antagonists (β Blockers) ❧

♥ Angiotension inhibitors
• ACE inhibitors (ACE-I) ❧
• Angiotensin receptor antagonists (ARBs)
• Direct Renin Inhibitors (DRIs)

♥ Vasodilators
♥ Calcium channel blockers (CCBs) ❧
♥ Other vasodilators

♫ = cardio-inhibitory drugs → ❏ cardiac remodeling
1st choice Antihypertensive Drugs: **Diuretics**

♥ 1st course of treatment

♥ Reduce blood volume & affect smooth muscle tone

♥ Types: Thiazide, Loop, and K+ sparing

• Diuretics trigger renin release, control with ACEI or ARB
1st choice Antihypertensive Drugs: Diuretics

**Thiazide-type**

- **Hydrochlorothiazide (Esidrix)**

  - **Indications**
    - Mild/moderate HTN and edema (of various types)
  
  - **ADRs**
    - Hypokalemia, pancreatitis, kidney failure, blood dyscrasias, respiratory distress, nausea (take with food to reduce), orthostatic hypotension, cross allergic reaction with other sulfonamides
    - May ↑ blood glucose, cholesterol, triglyceride, Ca^{++}, and uric acid levels

*Avoid >25mg/day in the elderly*
1<sup>st</sup> choice Antihypertensive Drugs:  
**Diuretics**

- **Loop Diuretics**
  - Furosemide (Lasix®) 
  - **Indications**
    - Edema associated with severe HTN, HF (CHF), renal insufficiency, etc.
  - **ADRs**
    - May cause deafness, use lowest possible dose. Inject slowly
    - Electrolyte imbalance and dehydration, yellow vision, cross allergic reaction with sulfonamides, ↑ blood glucose, gout, pancreatitis, blood dyscrasias
  - **Incompatibilities**
    - NSAIDS & ACEI → renal failure
    - Milrinone, diltiazem, Cipro, labetalol, etc, pH <7.0 → ppt

**PO, IV/IM**
**1st choice Antihypertensive Drugs:**

**Diuretics**

- **K⁺ sparing**
  - **Spironolactone 🏥 ⚫ C (Aldactone)**
    - **Indications**
      - Moderate HTN, CHF, edema
      - 1<sup>o</sup> aldosteronism
        - ⊗ aldosterone receptors
    - **ADRs**
      - Hyperkalemia, arrhythmias, gynecomastia (anti-androgen effects), gastric bleeding
      - Avoid K⁺ rich foods and K⁺ supplements
        - Citrus, bananas, dates, apricots, prunes, raisins, beets, spinach, beans, tomatoes, turkey, fish, beef

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**Boxed warning (S):** tumorigenic, not for initial therapy

**Don’t give with ACEI or ARBs**

**Others: amiloride and triamterene**

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A Beale

PHRM 203 - CV drugs 1 26
1st choice Antihypertensive Drugs: 
Diuretics used in surgery

❤️ Osmotic diuretics

- H₂O soluble non-electrolytes, freely filtered & poorly reabsorbed

- Common IV drip additive during trauma treatment or surgery - lots of blood loss may lead to renal infarction secondary to renal artery constriction.

- Example
  - Mannitol (Osmitrol)
2nd choice Antihypertensive Drugs: **Vasodilators**

♥ Vasodilators tend to cause greater compensation feedback than sympatholytics & are often combined with a diuretic

**Ca**++ **channel blockers** (CCB) ♥

**Amlodipine (Norvasc) 🌴**
- Indications
  - HTN & Angina (chronic stable and Prinzmetal’s) **PO**

**Diltiazem (Tiazac, Cardizem) 🌴**
- Indications
  - HTN & chronic stable & Prinzmetal’s angina **PO, IV**

**Verapamil (Covera HS) 🌴 🏵️ C**
- Indications
  - Slow IV – conversion of tachycardias; atrial fibrillation/flutter
  - PO – HTN, angina, arrhythmias **PO, IV**
3rd choice Antihypertensive Drugs:
Angiotensin inhibitors

- **ACE inhibitors** 👣 ⚖️ C/D

- Benazepril (Lotensin) 🎌, captopril (Capoten) 🎌, enalapril (Vasotec) 🎌, fosinopril, lisinopril, moexipril

  - ADRs - hypotension, DRY COUGH, hyperkalemia, kidney damage (especially with NSAID & diuretic), angioedema

  - Indications

    - **B** – HTN
    - **C** – HTN, HF, Lf vent dysfunction after MI, diabetic nephropathy
    - **E** – same as captopril

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ACEI ↑hypoglycemic effects of sulfonylurea drugs e.g., glyburide

Boxed warning for all ACEI, ARBs & DRIs: fetotoxicity!!

C – may cause blood dyscrasias
3\textsuperscript{rd} choice Antihypertensive Drugs: \textit{Angiotensin inhibitors}

- **Angiotensin receptor antagonists** $\text{C/D}$
  - Irbesartan (Avapro), Losartan (Cozaar), Valsartan (Diovan)

- **Indications**
  - \textbf{I} – HTN & diabetic nephropathy in DMT2
  - \textbf{L} – HTN, Lf vent. Hypertrophy, diabetic nephropathy
  - \textbf{V} – HTN, HF, MI

- **ADRs**
  - Significant orthostatic hypotension, anaphylactoid reactions including angioedema

\textit{Boxed warning for all ACEI, ARBs & DRIs: fetotoxicity!!}
3rd choice Antihypertensive Drugs: 
Angiotensin inhibitors

- **Direct Renin Inhibitor (DRI)**
  - **Aliskiren (Tekturna)**  
    - C/D

- **Indications**
  - HTN

- **ADRs & other info**
  - Significant orthostatic hypotension, anaphylactoid reactions including angioedema or SJS, hyperkalemia, peripheral edema. High doses dramatically increase risk of diarrhea.
  - In diabetics or in patients with GFR <60 ml/min, do NOT use in combo with ARBs or ACEIs.
  - Do NOT take with fatty food – establish a routine for taking it.
  
- **Boxed warning for all ACEI, ARBs & DRIs: fetotoxicity!!**
4th choice Antihypertensive Drugs: Vasodilators

- **Hydralazine (Apresoline)**  ![Switzerland]  ![Hospital] C
  - PO – HTN
  - Inj – Severe HTN
  - May cause a syndrome like lupus erythematosus

- **Nitroprusside (Nitropress)**  ![Switzerland]  ![Hospital] C
  - **Indications**
    - To induce an immediate BP drop
    - Acute congestive HF
    - To induce hypotension to reduce blood loss in surgery
  - **Boxed warnings:**
    1. must be diluted
    2. May cause precipitous BP drop
    3. May cause fatal cyanosis if used >10 min or high infusion rate

PO, IV, IM  
IV infusion after dilution

Not used alone
“Last” choice Antihypertensive Drugs: \( \beta \) blockers

\( \heartsuit \beta \) adrenergic receptor antagonists

- \( \downarrow \) BP by direct cardio effects: \( \downarrow \) HR and contractility (\( \Theta \) chronotropic and inotropic)
- \( \times \) Renin secretion \( \rightarrow \) \( \downarrow \) angiotensin II \( \rightarrow \) \( \times \) aldosterone
- \( \downarrow \) CNS sympathetic outflow

- **\( \beta_1 \) selective**
  - Atenolol, betaxolol, bisoprolol, esmolol, metoprolol (Lopressor, Toprol)
  - PO, IV

- **Nonselective \( \beta \) blockers**
  - Propranolol (Inderal) \( \heartsuit \), nadolol, pindolol, timolol
“Last” choice Antihypertensive Drugs: Sympatholytic drugs

**α₁ adrenergic receptor antagonists**

- Not used as much as β blockers
- Selective α₁ blockers

- **PO**
  - Doxazosin (Cardura), prazosin (Minipress), terazosin (Hytrin)
  - Block sympathetic arteriolar contraction
  - ADRs = orthostatic hypotension, fainting (1st dose syncope)

**General adrenergic inhibitors**

- Guanadrel (Hylorel)
  - Believed to displace NE from vesicles
- Guanethidin (Ismelin)
  - Blocks NE release
- Labetalol (Normodyne) and Carvedilol (Coreg)
  - α₁ and β non-selective receptor blocker

Okay for mild HTN, causes edema
"Last" choice Antihypertensive Drugs: Last ditch effort

📍Central agonists *(still sympatholytic!)*

📍 ↑ inhibitory CNS $\alpha_2$-adrenergic receptors which ↓ sympathetic tone (outflow)
📍 $\alpha_2$-adrenergic agonists can be blocked by TCAs
📍 Cause ↓ Cardiac Output by:
  - ↓ HR → Θ Chronotropic
  - ↓ Contractility → Θ Inotropic

– Methyl dopa (Aldomet®) 🍀 ☯ B PO/IV
  - Indication: HTN
  - ADR: may cause +Coombs test, hemolytic anemia, liver failure

– Clonidine (Catapres®) 🍀 ☯ C ☯ PO/Inj/Soln/Patch
  - Others, Guanabenz (Wytensin®) and Guanfacine (Tenex®)
  - Indications: HTN; with opiates for severe pain (epidural)
  - Discontinuation syndrome

Associated with:
- Sedation
- Depression
- Constipation & dry mouth
- Sexual dysfunction
- Sodium retention
“Last” choice Antihypertensive Drugs: Last ditch effort

- Peripheral DA (D₁) agonist
  - Fenoldopam (Corlopam) 
    - D₁ receptors in kidney, heart & mesentary → vasodilation
    - Indication
      - Short term (up to 48 hours in adults and 4 hours in kids) management of HTN
    - ADRs - reflex tachycardia, hypotension, ↑intraocular pressure. Contains sodium metabisulfite (may cause allergic reactions especially in asthmatics)
  - IV infusion
## Typical Fixed-Combination Drugs

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic name combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capozide</td>
<td>Hydrochlorothiazide with captopril</td>
</tr>
<tr>
<td>Combipres</td>
<td>Chlorthalidone with <em>clonidine</em></td>
</tr>
<tr>
<td>Hyzaar</td>
<td><em>Losartan</em> with <em>hydrochlorothiazide</em> 📌 📌 C/D</td>
</tr>
<tr>
<td>Inderide</td>
<td><em>Hydrochlorothiazide</em> with <em>propranolol</em> 📌</td>
</tr>
<tr>
<td>Lotrel</td>
<td><em>Amlodipine</em> with <em>benazepril</em> 📌 📌 C/D</td>
</tr>
<tr>
<td>Monopril-HCT</td>
<td>Fosinopril with <em>hydrochlorothiazide</em></td>
</tr>
<tr>
<td>Teczem ER Tablets</td>
<td><em>Enalapril</em> with <em>diltiazem</em></td>
</tr>
</tbody>
</table>

*Drugs in italics have been covered before*
Hypertension

Course of treatment

❤ Mild hypertension BP 120-139/80-89

❤ Lifestyle changes
  • Weight reduction
    ◆ Men 36” (Asian) - 40” waist
    ◆ Women 32” (Asian) - 35” waist
  • ↑ Exercise levels
    ◆ 30 - 60 minutes/day on most days
  • Diet changes
    ◆ DASH if possible
    ◆ Avoid alcohol, Na+
  • Avoid tobacco, quit smoking
  • Reduce stress

Treating hypertension in someone <65 yrs

• If lifestyle changes don’t decrease HT enough:
  Diuretics
  CCBs

• Lowest possible dose PO SID

• If not <140/90, or ADR too much, then add another drug or replace initial choice
Hypertension  

Courses of treatment

♥ Treating HTN in Diabetics
- Treatment usually starts at lower BP (130/80)
- Mild HTN recommendations 1st
  - Lifestyle changes
  - Weight
  - Exercise
  - Diet, DASH if possible
  - Quit smoking
  - Reduce stress
- If lifestyle changes don’t decrease HTN enough:
  1. ACE inhibitors
  2. Angiotensin receptor blockers (ARBs)

♥ In the Elderly
- Mild HTN rec.s 1st
- Diuretics - preferred
- CCBs
- Extreme care regarding multiple meds

♥ In those with heart disease history
- Mild HTN rec.s 1st
- ACE inhibitors
- Diuretics
- β blockers
- Usually given in combo formulations
Hypertension
Course of treatment

❤ HTN in pregnant women
• Mild hypertension recommendations first
• Careful monitoring before and after using meds
• Drugs of choice
  • Labetolol (Normodyne or Trandate) is 1st – mixed alpha/beta blocker
  • Methyl dopa (Aldomet) - central $\alpha_2$ - agonist
    (these are inhibitory neurons in the CNS)
• Extreme care regarding teratogenic potential of:
  • ACEI
  • Angiotensin II receptor inhibitors (ARBs)
  • Direct Renin Inhibitors

ACEI-related teratogenesis most likely related to a lack of amniotic fluid which leads to growth retardation – including lack of lung development, hypocalvarium, joint contractures, hypotension and death