Meet the Expert Handbook
Meet the Expert 1:

Christophe De Block (Belgium)
CONFLICT OF INTEREST

De Block Christophe

☐ I have the following potential conflicts of interest to report:

☐ Research Contracts
  ☐ Consulting
  ☐ Abbott Diagnostics, A. Menarini Diagnostics, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Novo Nordisk, Novartis, Roche Diagnostics, Sanofi

☐ Employment in the Industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☐ I declare that I have no potential conflict of interest.
Outline

1. Administering insulin: MDI vs CSII
2. Monitoring glucose: SMBG, Flash glucose monitoring, RT-CGM
3. Sensor-augmented pump therapy and the road towards the artificial pancreas
### Why pump therapy?

**Improved HbA$_{1c}$ control**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean difference 95% CI</th>
<th>Mean difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross-over trials</strong></td>
<td></td>
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<tr>
<td>Bruttomesso 2008</td>
<td>-0.10 [-0.43, 0.23]</td>
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<tr>
<td>Chiasson 1984 and 1985</td>
<td>0.40 [-0.58, 1.38]</td>
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<tr>
<td>Cohen 2003</td>
<td>-0.42 [-1.11, 0.27]</td>
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<tr>
<td>Hanaire-Broutin 2000</td>
<td>-0.35 [-0.62, -0.08]</td>
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<tr>
<td>Home 1982</td>
<td>-1.70 [-3.50, 0.10]</td>
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<tr>
<td>Hoogma 2005</td>
<td>-0.22 [-0.38, -0.06]</td>
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<tr>
<td>Nathan 1982</td>
<td>2.48 [-3.86, -1.10]</td>
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<tr>
<td>Saubrey 1988</td>
<td>0.00 [-0.31, 0.31]</td>
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<tr>
<td>Schmitz 1989</td>
<td>-0.70 [-1.94, 0.54]</td>
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<tr>
<td>Weintrob 2004</td>
<td>-0.20 [-0.59, 0.19]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>-0.25 [-0.45, -0.05]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Parallel trials</strong></td>
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<tr>
<td>DeVries 2002</td>
<td>-0.80 [-1.65, 0.05]</td>
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<tr>
<td>Doyle 2004</td>
<td>-0.90 [-1.68, -0.12]</td>
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<tr>
<td>Lepore 2003</td>
<td>0.30 [-0.53, 1.13]</td>
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<tr>
<td>Meschi 1982</td>
<td>0.20 [-1.94, 2.34]</td>
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<tr>
<td>Nosadini 1988</td>
<td>-0.80 [-1.35, -0.25]</td>
<td></td>
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<tr>
<td>Nuboer 2008</td>
<td>-0.48 [-0.90, -0.06]</td>
<td></td>
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<tr>
<td>Oslo Study 1985 to 1992</td>
<td>-0.40 [-1.51, 0.71]</td>
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<tr>
<td>Pozzilli 2003</td>
<td>0.10 [-0.31, 0.51]</td>
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<tr>
<td>Skogsberg 2008</td>
<td>-0.20 [-0.42, 0.02]</td>
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<tr>
<td>Tsui 2001</td>
<td>0.25 [-0.18, 0.68]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>-0.26 [-0.52, -0.00]</strong></td>
<td></td>
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</tbody>
</table>

**Total (95% CI):** -0.25 [-0.40, -0.10]

Heterogeneity: $\tau^2=0.04$; $\chi^2=37.68$, df=19 ($p=0.007$); $I^2=50\%$

Test for overall effect: $Z=3.25$ ($p=0.001$)

CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections

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**Cochrane Database Syst Rev 2010;20:CD005103**
Why pump therapy?
Less severe hypoglycaemia

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Favours CSII</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruttomesso 2008</td>
<td></td>
<td>2.11 (0.23, 19.34)</td>
</tr>
<tr>
<td>Cohen 2003</td>
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<td>0.16 (0.01, 2.05)</td>
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<td>DiMeglio 2004</td>
<td></td>
<td>0.84 (0.05, 14.57)</td>
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<tr>
<td>Doyle 2004</td>
<td></td>
<td>0.08 (0.004, 1.34)</td>
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<tr>
<td>Fox 2005</td>
<td></td>
<td>0.17 (0.01, 3.88)</td>
</tr>
<tr>
<td>Hirsh 2005</td>
<td></td>
<td>0.66 (0.08, 5.50)</td>
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<tr>
<td>Hoogma 2006</td>
<td></td>
<td>0.48 (0.06, 3.52)</td>
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<tr>
<td>Lepore 2003</td>
<td></td>
<td>0.62 (0.05, 7.62)</td>
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<tr>
<td>Opipari-Arrigan 2007</td>
<td></td>
<td>0.15 (0.01, 4.68)</td>
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<tr>
<td>Thomas 2007</td>
<td></td>
<td>1.00 (0.05, 21.44)</td>
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<tr>
<td>Weintrob 2003 and 2004</td>
<td></td>
<td>0.30 (0.03, 3.43)</td>
</tr>
<tr>
<td>Wilson 2005</td>
<td></td>
<td>1.13 (0.06, 21.09)</td>
</tr>
</tbody>
</table>

**Pooled odds ratio**

0.48 (0.23, 1.00)

CI, confidence interval; CSII, continuous subcutaneous insulin infusion
Why pump therapy?
Less CVD and mortality

- Setting: Swedish National Diabetes Register, Sweden 2005–2012
- Participants: 18,168 people with type 1 diabetes, 2441 using CSII and 15,727 using MDI

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CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; MDI, multiple daily injections.
Intermittent scanning: Freestyle Libre: flash glucose monitoring

Abbott FreeStyle Libre meter  
sensor & applicator  
software  
PATIENT
FS Libre: 3 key data

1. Present glucose
   - Current glucose level: 112 mg/dL

2. Past 8h glucose profile

3. Predicted trend
## Interpretation of arrows in different systems

<table>
<thead>
<tr>
<th>Devices</th>
<th>Freestyle Libre and Eversense</th>
<th>Dexcom G5/G6</th>
<th>Guardian Connect</th>
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</thead>
<tbody>
<tr>
<td>Arrow</td>
<td>meaning</td>
<td>Arrow</td>
<td>Arrow</td>
</tr>
<tr>
<td>↑</td>
<td>increasing &gt; 2 mg/dl/min or &gt; 0.1 mmol/l/min</td>
<td>↑↑↑</td>
<td>increasing &gt; 3 mg/dl/min or 0.17 mmol/l/min</td>
</tr>
<tr>
<td>↑↑</td>
<td>increasing 1-2 mg/dl/min or 0.06-0.1 mmol/l/min</td>
<td>↑</td>
<td>increasing 2-3 mg/dl/min or 0.1-0.17 mmol/l/min</td>
</tr>
<tr>
<td>→</td>
<td>stable</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>↓</td>
<td>decreasing 1-2 mg/dl/min or 0.06-0.1 mmol/l/min</td>
<td>↓</td>
<td>decreasing 1-2 mg/dl/min or 0.06-0.1 mmol/l/min</td>
</tr>
<tr>
<td>↓</td>
<td>decreasing &gt; 2 mg/dl/min or &gt; 0.1 mmol/l/min</td>
<td>↓</td>
<td>decreasing 2-3 mg/dl/min or 0.1-0.17 mmol/l/min</td>
</tr>
<tr>
<td>↓</td>
<td>decreasing &gt; 3 mg/dl/min or 0.17 mmol/l/min</td>
<td>↓↓</td>
<td>decreasing &gt; 3 mg/dl/min or 0.17 mmol/l/min</td>
</tr>
<tr>
<td>↓↓</td>
<td>decreasing &gt; 3 mg/dl/min or 0.17 mmol/l/min</td>
<td>↓↓↓</td>
<td>decreasing &gt; 3 mg/dl/min or 0.17 mmol/l/min</td>
</tr>
</tbody>
</table>

Interpretation of arrows as used in different systems. De Ridder F, den Brinker M, De Block C, Therap Advances Endocrinol & Metab 2019; in revision.
Interpretation of FGM

Retrospective
Visit at the educator & physician
**Snapshot**
24 september 2015 - 7 oktober 2015 (14 dagen)

**Glucose**

- **GEMIDDELDE GLUCOSE**: 174 mg/dL
  - % boven doel: 64%
  - % binnen doel: 28%
  - % onder doel: 8%

- **Hypo's**: 13
  - Gemiddelde duur: 01 min

**Genoteerde KH**

- **DAGELIJKE KH**: 5,0 per 1000 dag

**Genoteerde insuline**

- **Snelwerkende insuline**: 15,1 eenheden/ dag
- **Maaltijd**: 12,5 eenheden/ dag
- **Corractia**: 2,6 eenheden/ dag
- **Gebruikerswijziging**: 0,0 eenheden/ dag
- **Handmatig geadministratie**: 0,0 eenheden/ dag
- **Langwerkende insuline**: 15,1 eenheden/ dag

**TOTALE DAGELIJKE INSULINE**: 15,1 eenheden/ dag

**Sensorgebruik**

- **Geregistreerde sensorgegevens**: 94%
  - Dagelijkse scans: 14

**Opmerkingen**

- Haten aangetroffen in de insulinegegevens. Deze rapportageperiode bevat 1 dag zonder vastgelegde insulinevoorzieningen.
- Haten aangestoten in voedselgegevens.

Deze rapportageperiode bevat 1 dag zonder vastgelegde voedselvoorzieningen.
Snapshot
24 september 2015 - 7 oktober 2015 (14 dagen)

**Glucose**
- **Geschatte HbA1c**: 7.7% of 61 mmol/mol

**TIR, personalized**

**HYPOS**
- 13
- Gemiddelde duur: 91 min

**Sensorgebruik**
- Geregistreerde sensorgegevens: 94%
- Dagleijke scans: 14

**Opmerkingen**
- Hiten aangeroepen in de insulinegegevens. Deze rapportageperiode bevat 1 dag zonder vastgelegde insulinevoorzieningen. • Hiten aangeroepen in voedselgegevens. Deze rapportageperiode bevat 1 dag zonder vastgelegde voedselvoorzieningen.

Correct?
- **DAGELIJKE KH**: 5.0
- **Genoteerde insuline**: 15.1
- **TOTALE DAGELIJKE INSULINE**: 15.1

Not Correct
Interpretation of FGM

1. check for **adequate data:**
   - at least 14 days to allow for patterns and variability to be visualised
   - nr of scans
   - percentage capture

2. look for patterns of **low** glucose:
   - fasting vs postprandial (after every meal of one specific meal)
   - carb counting correct? ICR needs adaptation?
   - after correction bolus? ISF correct?
   - after exercise
   - hypo fear/anxiety

3. look for patterns of **high** glucose levels
   - nocturnal vs through the day
   - postprandial (after every meal of after one specific meal)
   - before going to bed?
   - snacking; defensive eating (fear of hypo at night)
   - too many carbs, improper ICR
Interpretation of FGM

4. look for areas of wide glucose **variability**
   - timing & amount
   - fluctuating meal patterns/times
   - different times of physical activity

5. **mark up** the AGP report: note factors that may affect the management plan:
   - note time of insulin injections, food intake, exercise
   - working days vs weekend days; shift work

6. ask the **patient**: “what do you see?”: shared decision making; personalised medicine, visual learning

7. **compare** to past AGP and reinforce successful strategies
   - better stability – less variability helps to build confidence for the patient
   - compare improvement of TIR, reduction of time in hypo/hyper
   - check eA1c or GMI (glucose management indicator)

8. agree on **action plan** with patient: **shared** decision making
   - set goals; time in range (personalize)
   - empower the patient
**Casus 1**

woman °1986

**history**
- 1997: type 1 diabetes mellitus

**anamnesis**
- Started exercising, experiences fluctuating glucose values
- No frequent hypo’s; moderate hypoglycaemia-unawareness.

- 81 kg - 175 cm
- HbA1c: 9.1%
- Diabetes medication: Levemir 22 E - 24 E; Novorapid 10+10+10E
**Snapshot**
11 januari 2017 - 7 februari 2017 (28 dagen)

**Glucose**

<table>
<thead>
<tr>
<th>Gemiddelde glucose</th>
<th>209 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>% boven doel</td>
<td>69 %</td>
</tr>
<tr>
<td>% binnen doel</td>
<td>20 %</td>
</tr>
<tr>
<td>% onder doel</td>
<td>11 %</td>
</tr>
</tbody>
</table>

**Hypo's**

| Gemiddelde duur | 120 Min |

**Sensoregebruik**

<table>
<thead>
<tr>
<th>Geregistreerde sensorgegevens</th>
<th>62 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dagelijkse scans</td>
<td>3</td>
</tr>
</tbody>
</table>

**Geschatte HbA1c** 8,9% of 74 mmol/mol

**Genoteerde KH**

**Genoteerde insuline**

- DAGELIKSE KH
- DAGELIKSE INSULINE

**Opmerkingen**
• 8,9% estimated A1c over 1 month
• 3 scans/d
• Registered scan data 62%
• No data on insulin doses or meals
• Clear pattern: hypo at breakfast, high everywhere else
Diabetes medication: Levemir 22 E - 24 E; Novorapid 10+10+10E
What would you do?
Pattern analysis

• High values before going to bed:
  • She gives a correction bolus resulting in hypoglycaemia 5-6 hours later

• First night: relative stable but no correction bolus given

• This has nothing to do with basal insulin dose
Casus 2

- Woman °1966

**History**
- Type 1 since 1971

**anamnesis**
- Feels good, reports no problems
- Hypo’s after biking. Moderate hypoglycaemia-unawareness.

- Humalog 4 – 4à6 – 6à8 U; Lantus 12U
- 60 kg - 169 cm
- HbA1c: 6.9%
Snapshot
4 januari 2017 - 17 januari 2017 (14 dagen)

Glucose

GEMIDDELDE GLUCOSE 137 mg/dL
% boven doel 43%
% binnen doel 37%
% onder doel 20%

Hypo's 31
Gemiddelde duur 121 Min

Genoteerde KH

DAGELIJKSE KH

Genoteerde insuline

Snelwerkende insuline 15,3 eenheden/ dag
Langwerkende insuline 12,2 eenheden/ dag
TOTALE DAGELIJKSE INSULINE 27,5 eenheden/ dag

Sensorgebruik

GEREGISTREERDE SENSORGEGEVEN@

94%

Dagelijkse scans 12

Opmerkingen
Decreasing trend during night

Before going to bed: okay => not a problem of overcorrecting, but too much basal insulin

Always look at glucose levels before going to bed... and ask patients whether they correct for high values by giving an extra bolus...
Look at individual days for detailed discussion

Overcorrection of hypo and of hyper
Postprandial values are lower than preprandial values

Resulting in hypoglycaemia
Interpretation of FGM

Prospective – real time
Each moment of the day/night for the patient
Format of answer

1. Reflection / Cause? / Essential questions

2. Immediate action

3. Future actions / How to prevent? / What to do next time?
concrete situations: what should a patient do if ...

1. 1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow

2. 90 minutes before a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L)

3. The patient’s glycaemia is 90 mg/dl (5 mmol/L) before bedtime, with a flat arrow

4. The patient wakes up and notes that he/she had hypo’s during the night

5. 2h after a meal, the patient’s glycaemia is 90 mg/dl (5 mmol/L) with 90° decreasing arrow

6. Patient had a hypo; 15 min after eating, the patient’s glycaemia is still low
Situation 1
1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow → what should the patient do?

Reflection

• Forgot to inject before meal?
• Something wrong with injection technique? injected in lipodystrophy?
• Ate more than initially thought? (not enough insulin injected in relation to the amount of carbohydrates)
• Sickness?
Situation 1
1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow → what should the patient do?

Immediate action

- In case you have forgotten to inject or in case you have eaten more than initially thought : inject immediately
  - How many units? ~ICR and CF
Situation 1
1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow → what should the patient do?

Immediate action

- In other cases: be careful and don’t inject immediately! As glycaemia levels peak 60-90 min after start of the meal (depends also on what you have eaten, eg fat delays gastric emptying), it is recommended to wait and flash again 120 min (2 hours) after start of the meal.
- If still high 120 min (2 hours) after start of the meal, injection of a correction dose can be considered.
**Situation 1**
1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow → what should the patient do?

**Immediate action**
- Glucose 1h after breakfast: 240 mg/dl with 45° increasing arrow : 30 minutes later 249 mg/dl with decreasing arrow: no action taken. Normal glucose excursion after a meal. Perfect glucose value before next meal
- In the evening: almost same situation
- Cave: direction of the arrows can change within 15-30 minutes
Situation 1
1h after a meal, the patient’s glycaemia is 250 mg/dl (14 mmol/L) with an 45° increasing arrow → what should the patient do?

Future
• If this occurs frequently, consider:
  • Injecting the meal-time insulin earlier before the start of the meal (e.g. 15–20 min before the meal for rapid-acting insulins instead of just before the meal) or
  • Injecting a faster acting insulin
• This needs to be discussed with your diabetes team
Situation 2
90 minutes before a meal, the patient’s glycaemia is 250 mg/dL (14 mmol/L) → what should the patient do?

Reflection

– Did I recently eat a snack (without injecting)?
– How much time has passed since the last injection?
– Did I recently have a hypo?
– Have I just done strenuous exercise?
– Will I do exercise in the coming hours (e.g. cycle home from work)?
– Sickness?
– What is the direction of the trendline?
Immediate action

- You may consider a correction dose, but be careful because you could react very sensitively to insulin as quite some time has passed since the last meal (no carbohydrates in the stomach anymore)
- Before the next meal: don’t correct for high values

Patient HbA1c 6.8% prior to start FGM, now 6.4%

90 min before lunch 250 mg/dL
Situation 2
90 minutes before a meal, the patient’s glycaemia is 250 mg/dL (14 mmol/L) → what should the patient do?

Immediate action

• You may consider a correction dose, but be careful because you could react very sensitively to insulin as quite some time has passed since the last meal (no carbohydrates in the stomach anymore)

• Before the next meal: don’t correct for high values

- 90 min before lunch: 250 mg/dL
- Correction factor: 50
- Gave a correction bolus: 2U
- Glucose 90 min later: 155 mg/dL
Situation 3
The patient’s glycaemia is 90 mg/dL (5 mmol/L) before bedtime, with a flat arrow → what should the patient do?; does the patient need to eat?
Situation 3
The patient’s glycaemia is 90 mg/dL (5 mmol/L) before bedtime, with a flat arrow → what should the patient do?; does the patient need to eat?

Reflection

• Did you do physical activity (doesn’t necessarily mean sports 😊) in the late afternoon or evening? → If yes, know that your glycaemia risks decreasing further

• What do the FGM results of the previous evenings say? What are the daily trends of the last 7 days? Do you easily experience hypos in the early night? → If yes, then do not put blind faith in the trendline. Many patients experience decreasing glycaemia levels in the early night.

• Are you aware of nocturnal hypos?

• Was your carbohydrate intake at dinner low compared to bolus insulin dose?
Situation 4
The patient wakes up in the morning and notes that he/she had hypo’s during the night → what should the patient do?

\[ \text{Reflection} \]

*Important to think about a possible explanation, because hypo you haven’t been aware of this hypo during the night!*
**Situation 4**
The patient wakes up in the morning and notes that he/she had hypo’s during the night → what should the patient do?

**Reflection**

- Did the hypo appear **early** (less than 5 hours after dinner) or **late** in the night (more than 5 hours after dinner)?
  - **In case of an hypo in the early night**, think about the following:
    - Was the carbo intake at dinner lower than usual, and lower compared with the insulin bolus?
    - Did you do exercise in the late afternoon or evening?
    - Did you drink alcohol?
    - Did you inject the wrong insulin (rapid-acting instead of basal)?
    - Did you give an extra bolus injection during the night?

  - **In case of an hypo in the late night**, think about the following:
    - Have you injected a too high dose of basal insulin at night?

- **Is there a repetitive pattern?**
  - Check the trends of the last 7 days to know whether this frequently occurs.
Situation 5
2h after a meal, the patient’s glycaemia is 90 mg/dL (5 mmol/L) with 90° decreasing arrow → what should the patient do?

Reflection

• Have you done exercise?
• Have you eaten less carbohydrates than usual?
• Have you injected too much meal-time insulin?
Immediate action
• Consider this as a hypo. The FGM measurement shows the result from approximately 10–15 minutes ago; at that moment, your glycaemia was 90 mg/dl and was decreasing quickly
• Eat fast sugar first (e.g. 3–4 dextro sugar tablets) to correct the hypo and then slow sugar (e.g. cereal biscuit or fruit) to avoid your blood sugar decreasing again after a while
• Don’t over-correct
• Be aware that the FGM monitoring is not the best technique to see that the hypo is over. Rely on your symptoms or on fingersticks

Future
• If this occurs frequently, consider lowering the insulin dose before the meal
Situation 6
patient had a hypo; 15 min after taking sugar, the patient’s scanned glucose level is still low → what should the patient do?

Reflection

▪ The subcutaneous measurement with the sensor runs 10 to 15 min behind of what is happening in the blood (lag time). So, don’t continue to eat sugar until the sensor value is OK, because that would lead to substantial over-correction of hypoglycemia!

▪ Do you feel any symptoms of hypoglycaemia?
Outline

1. Administering insulin: MDI vs CSII
2. Monitoring glucose: SMBG, Flash glucose monitoring, RT-CGM
3. Sensor-augmented pump therapy and the road towards the artificial pancreas
CGM systems currently available

**Enzymatic (glucose oxidase)**
- Dexcom G5 Platinum S.A.
- Abbott FreeStyle Navigator 2
- Medtronic Guardian Connect

**Non-enzymatic (fluorescence)**
- Eversense™ Long-term glucose sensor

**Stand-alone devices**
- Devices used in combination with insulin pumps
- Medtronic Paradigm Veo
- Medtronic 640G
- Medtronic 670G
Threshold-based insulin-pump interruption for reduction of hypoglycemia

ASPIRE-In home study

Threshold-based insulin-pump interruption for reduction of hypoglycemia

ASPIRE – In home study

**HbA1c**

<table>
<thead>
<tr>
<th>Glycated hemoglobin (%)</th>
<th>Threshold-suspend group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>At randomization</td>
<td>7.26 ± 0.71</td>
<td>7.24 ± 0.67</td>
</tr>
<tr>
<td>At 3 months</td>
<td>7.21 ± 0.77</td>
<td>7.14 ± 0.77</td>
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**Mean AUC for Nocturnal Hypoglycemic Events**

Run-in phase

<table>
<thead>
<tr>
<th>Threshold-suspend group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1547 ± 2035</td>
<td>1406 ± 1950</td>
</tr>
</tbody>
</table>

Study phase

<table>
<thead>
<tr>
<th>Threshold-suspend group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>980 ± 1200</td>
<td>1568 ± 1995</td>
</tr>
</tbody>
</table>

38% reduction

P<0.001

n = 247 T1DM

Predicted low glucose management (SmartGuard®)

PLGM = SmartGuard®: Algorithm for predictive low glucose management

![Graph showing glucose levels and time of day](image)

Suspension of insulin infusion

“Threshold low”

After insulin infusion is resumed, ≥30 min must pass before a consecutive suspension may occur

PLGM, predictive low glucose management.
Objective: To assess impact of RT-CGM in real-world settings on glycemic control, hospital admissions, work absenteeism, and quality of life (QOL).

Design: Prospective, observational, multicentre, cohort study.

Participants: 515 adults with T1DM on CSII. 47% had impaired awareness of hypoglycaemia.
Background: Effect of CGM on glycaemic control, acute admissions and quality of life: a real-world study in adults

Change in HbA$_1c$ from baseline

Baseline: 7.7 ± 0.9%
12 months: 7.4 ± 0.8%  
$p<0.0001$

Admission to the hospital for severe hypoglycaemic or ketoacidosis episodes

Year before reimbursement  
16%  
Year after reimbursement  
4%  
$p<0.0005$

Reduction in hospitalisation days from 53.5 to 17.8 days per 100 patient-years

Quality of life improved significantly, with a strong decline in fear of hypoglycaemia

Baseline:
HbA$_1c$: 7.7 ± 0.9%
12 months:
HbA$_1c$: 7.4 ± 0.8%

Change in HbA$_1c$ from baseline:

% in hypo:
Pre: 12  
1 M: 11.8  
4 M: 9.5  
8 M: 8.8  
12 M: 8.3  
12 M: 7.6  
***$p<0.001$

$\Delta -4.2\%$
Minimed 670 G

HYBRID CLOSED LOOP SYSTEM
THE ADVANTAGE OF DOSING AUTOMATION

Journey Towards Artificial Pancreas Technology
- Advanced Algorithm
- Enlite® 3 Sensor
- New Pump Platform

DESIGNED TO:
- Suspend Insulin delivery on predictive low glucose level
- Adjust Basal Insulin delivery in response to high glucose level
- 24 Hour Dosing

POTENTIAL BENEFITS:
- Reduce A1c
- Improve Time in Range
- Reduce Patient Burden

Status
- Pivotal trial enrollment early completion
- 80% of study participants opted for continued access
- PMA submission by end of June 2016
THE MINIMED™ 670G SYSTEM AUTOMATICALLY ADJUSTS BASAL INSULIN\(^1,2\) TO HELP OPTIMISE TIME IN RANGE

THROUGHOUT THE DAY, INSULIN NEEDS VARY

Traditional pump therapy delivers pre-programmed, fixed basal rates, with variable glucose results.

Self-adjusting SmartGuard™ technology provides more consistent glucose results, helping to optimise time in range.\(^1,2\)

---

Medtronic MiniMed 670G – approved by FDA in September 2016 – on the market spring 2017

Automatically controlled by the system:
- Fixed target at **120 mg/dL (6.7 mmol/L)**
- Basal insulin is controlled day and night (24 hours) by the algorithm
- Basal insulin is adapted according to glucose sensor
- Thresholds for insulin delivery (both low & high)
- Frequent checks of system and sensor integrity

The patient has to:
- Enter the carbohydrate content of meals
- Undergo blood glucose testing for **calibration**
- Change sensor and infusion set
SMARTGUARD™ AUTOMODUS

BOLUS

Set up
1. Insulin-carb ratio (in grams)
2. Active insulin time

Meal bolus
- preprogrammed ICR & nr of grams of CHO
- only normal bolus (no square of dual wave bolus)

Correction bolus (target 8,3 mmol/l [150 mg/dl])
- Correction dose is proposed by the algorithm
- ISF (insulin sensitivity factor) is determined by the algorithm
- Uses the active insulin time (insulin on board)
  - (recommendation: 3-4 hr)
### Basaal

<table>
<thead>
<tr>
<th>24-uurs totaal</th>
<th>24-uurs totaal</th>
<th>24-uurs totaal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tijd</td>
<td>E/H</td>
<td>Tijd</td>
</tr>
<tr>
<td>00:00</td>
<td>0,850</td>
<td>--</td>
</tr>
<tr>
<td>03:00</td>
<td>0,500</td>
<td>--</td>
</tr>
<tr>
<td>06:00</td>
<td>0,850</td>
<td>--</td>
</tr>
<tr>
<td>08:00</td>
<td>0,500</td>
<td>--</td>
</tr>
<tr>
<td>09:00</td>
<td>0,050</td>
<td>--</td>
</tr>
<tr>
<td>15:00</td>
<td>0,500</td>
<td>--</td>
</tr>
<tr>
<td>19:00</td>
<td>0,550</td>
<td>--</td>
</tr>
<tr>
<td>20:00</td>
<td>0,300</td>
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</tr>
</tbody>
</table>

### Basaal 2

<table>
<thead>
<tr>
<th>Tijd</th>
<th>E/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

### Basaal 3

<table>
<thead>
<tr>
<th>Tijd</th>
<th>E/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

### Bolus

- **Bolus Wizard**: Aan
- **Eenh.**: g, mg/dl
- **Actieve-insulinetijd (h:mm)**: 3:00
- **Max bolus**: 10,0 E
- **Bolusstapgroottes**: 0,1 E
- **Bolussenheid**: Standard
- **Dual/Square**: Aan/Aan

### KH-ratio (E/EQ)

<table>
<thead>
<tr>
<th>Tijd</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>1,2</td>
</tr>
<tr>
<td>5:30</td>
<td>1,5</td>
</tr>
<tr>
<td>11:00</td>
<td>1,9</td>
</tr>
<tr>
<td>16:00</td>
<td>1,3</td>
</tr>
</tbody>
</table>

### Insulinegevoeligheid (mg/dl per E)

<table>
<thead>
<tr>
<th>Tijd</th>
<th>Gevoelig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>60</td>
</tr>
<tr>
<td>5:30</td>
<td>70</td>
</tr>
<tr>
<td>11:00</td>
<td>80</td>
</tr>
</tbody>
</table>

### Streef-BG (mg/dl)

<table>
<thead>
<tr>
<th>Tijd</th>
<th>Laag</th>
<th>Hoog</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>
Key Messages

- Greater patient (& team) involvement in the initial phase:
  - target = 120 mg/dl (and not lower)
  - calibrations need to be meticulous: requires extensive fingersticking
  - carb counting in grams need to be as exact as possible
  - ICR increases in most patients
  - boluses:
    - only normal boluses are delivered; no square wave of dual wave
    - correction bolus: accept or not, not able to overrule, only possible > 150 mg/dl
    - initially correction for high takes forever... self-learning system: do not use phantom carbs
  - challenges:
    - sports: half bolus before commencing exercise? Temporary target of 150 mg/dl after exercise?
    - pregnancy? (pre 90 vs PPG 130 mg/dl)
    - meals rich in fat and carbs: French fries... 2x half a bolus (before and after)?
Correction bolus: self-adapting
Conclusion: a system for every patient

- 99 of 120 (80%) participants of the pivotal trial are continuing to use the HCL device even prior to FDA approval
- Patients with severe hypoglycaemia or hypo unawareness
- Children and adolescents
- Preschool children

- Continuous glucose monitoring with/without CSII
  - Hypoglycaemia unawareness
  - Competitive athletes
  - Pregnancy

- Flash glucose monitoring
  - Improve “time in range”
  - Improve quality of life

- Blood glucose self-monitoring
  - Great point accuracy
  - No complete picture of glucose values

HCL, hybrid closed loop. FDA, Food and Drug Administration (USA) 
Courtesy of prof Thomas Danne
Meanwhile: Don’t let diabetes stop you
Thank you for your attention
Meet the Expert 10:

Eda Ertorer (Turkey)
NCAH AND FEMALE REPRODUCTION
M. Eda Ertorer
Baskent University Faculty of Medicine
Division of Endocrinology
Adana/Turkiye
ECE 2019-Lyon/France
Nothing to disclose
Congenital adrenal hyperplasia (CAH)
Autosomal recessive disease is caused by the loss or severe decrease in activity in enzymatic steps for cortisol biosynthesis
Clinical features related to gonadal function in women with CAH.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Androgen excess</th>
<th>CAH group</th>
<th>Estrogen deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>21OH</td>
<td>11OH</td>
<td>3bHSD</td>
</tr>
<tr>
<td>Gene</td>
<td>CYP21A2</td>
<td>CYP11B1</td>
<td>HSD3B2</td>
</tr>
<tr>
<td>Elevated precursor</td>
<td>17OHP</td>
<td>DOC, 11-deoxycortisol</td>
<td>17OHP-Freg</td>
</tr>
<tr>
<td>External genitalia</td>
<td>Virilized</td>
<td>Virilized</td>
<td>Normal</td>
</tr>
<tr>
<td>Pubertal development</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent or incomplete</td>
</tr>
</tbody>
</table>

Various forms of CAH known to impact on reproduction.

| Congenital lipoid hyperplasia   |
| 17a-Hydroxylase/17,20-lyase deficiency |
| 3b-HSD deficiency               |
| 11b-Hydroxylase deficiency      |
| P450 Oxidoreductase deficiency  |
| 21-hydroxylase deficiency       |

21OHD responsible for 90–95% of CAH cases

- Over 200 CYP21A2 mutations
- 10-12 mutations constitute most cases
CAH-21OHD
(depending on the enzymatic activity of 21OH)

Classical Salt-wasting (SW)

Classical Simple-virilizing (SV)

Nonclassical forms (NCAH)
Mechanisms of androgen excess in NCAH pts:

*Adrenal hyperactivity due to altered enzyme kinetics
  (mostly without high ACTH levels)
  -Adrenal androgen secretion and its response to ACTH are increased

*Increased ovarian androgen secretion causing PCOS-like phenotype
  -High adrenal progesterone and androgens—HPO axis disruption --rapid GnRH pulse frequency and LH hypersecretion

*Increased peripheral conversion of circulating high levels of steroid metabolites (progesterone-17OHP) to potent androgens

NCAH AND FEMALE REPRODUCTION

Learning objectives and outline of my presentation

- What are the epidemiological aspect and genetic background?
- What are the clinical outcomes?
- Why is genetic analysis important?
- What are the theraupeutical approaches?
Case 1
18 years old woman admitted with the complaint of hirsutismus
She had regulary menses
Nothing special about her past medical history
Her physical examination revealed normal findings except the Ferriman Galleway score 12

Laboratory analyses
Serum TSH-Prolactin-Normal
Testosterone- Androstenodione-Mildly elevated
Follicular phase-early morning-17-OH progesterone=4.3ng/ml
ACTH-stimulated 17-OH progesterone = 13.8ng/ml

**Diagnostic Criteria**
Baseline 17-OH progesterone > 2.0 ng/ml  
Stimulated 17-OH progesterone > 10.0 ng/ml

**NCAH due to 21OHD**
The active gene: 21B and the pseudogene: 21A

<table>
<thead>
<tr>
<th>Exon/intron</th>
<th>Mutation type</th>
<th>Mutation</th>
<th>Phenotype</th>
<th>Severity of enzyme defect (% enzyme activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclassical mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 1</td>
<td>Missense mutation</td>
<td>P30L</td>
<td>NC</td>
<td>Mild (30–60%)</td>
</tr>
<tr>
<td>Exon 7</td>
<td>Missense mutation</td>
<td>V281L</td>
<td>NC</td>
<td>Mild (20–50%)</td>
</tr>
<tr>
<td>Exon 8a</td>
<td>Missense mutation</td>
<td>R339Ha</td>
<td>NC</td>
<td>Mild (20–50%)</td>
</tr>
<tr>
<td>Exon 10a</td>
<td>Missense mutation</td>
<td>P453Sa</td>
<td>NC</td>
<td>Mild (20–50%)</td>
</tr>
<tr>
<td>Classical mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion</td>
<td>30-kb deletion</td>
<td></td>
<td>SW</td>
<td>Severe (0%)</td>
</tr>
<tr>
<td>Intron 2</td>
<td>Aberrant splicing of intron 2</td>
<td>656 A/C-G</td>
<td>SW, SV</td>
<td>Severe (ND)</td>
</tr>
<tr>
<td>Exon 3</td>
<td>Eight-base deletion</td>
<td>G110 Δ8nt</td>
<td>SW</td>
<td>Severe (0%)</td>
</tr>
<tr>
<td>Exon 4</td>
<td>Missense mutation</td>
<td>I172N</td>
<td>SV</td>
<td>Severe (1%)</td>
</tr>
<tr>
<td>Exon 6</td>
<td>Cluster</td>
<td>I236N, V237E, M239K</td>
<td>SW</td>
<td>Severe (0%)</td>
</tr>
<tr>
<td>Exon 8</td>
<td>Nonsense mutation</td>
<td>Q318X</td>
<td>SW</td>
<td>Severe (0%)</td>
</tr>
<tr>
<td>Exon 8</td>
<td>Missense mutation</td>
<td>R356W</td>
<td>SW, SV</td>
<td>Severe (0%)</td>
</tr>
<tr>
<td>Exon 10a</td>
<td>Missense mutation</td>
<td>R483Pa</td>
<td>SW</td>
<td>Severe (1–2%)</td>
</tr>
</tbody>
</table>
CAH-21OHD
(depending on the enzymatic activity of 21OH)

Classical Salt-wasting (SW)
Classical Simple-virilizing (SV)
Nonclassical forms (NCAH)
-10 mutations and deletion represent > 90% of NCAH carry a point mutation.
## Concordance btwn phenotype and genotype

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Clinical severity</th>
<th>Phenotype</th>
<th>Enzyme activity (in vitro) Percentage of normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td></td>
<td>SW</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Deletion</td>
<td></td>
<td>SW</td>
<td></td>
</tr>
<tr>
<td>Del 8 bp E3</td>
<td></td>
<td>SW/SV</td>
<td></td>
</tr>
<tr>
<td>Cluster E6</td>
<td></td>
<td>SV</td>
<td>2-10%</td>
</tr>
<tr>
<td>L307insT</td>
<td></td>
<td>SV</td>
<td>2-10%</td>
</tr>
<tr>
<td>Q318X</td>
<td></td>
<td>SV/NCAH</td>
<td></td>
</tr>
<tr>
<td>R356W</td>
<td></td>
<td>NCAH</td>
<td>30-50%</td>
</tr>
<tr>
<td>I2 splice</td>
<td></td>
<td>SW/SV</td>
<td></td>
</tr>
<tr>
<td>I172N</td>
<td></td>
<td>SV</td>
<td>2-10%</td>
</tr>
<tr>
<td>P30L</td>
<td></td>
<td>SV/NCAH</td>
<td></td>
</tr>
<tr>
<td>V281L</td>
<td></td>
<td>NCAH</td>
<td>30-50%</td>
</tr>
<tr>
<td>P453S</td>
<td></td>
<td>NCAH</td>
<td>30-50%</td>
</tr>
</tbody>
</table>

### Concordance btwn phenotype and genotype

- **100% for SW form**
- **95% for SV form**
- **70% for NCAH form**

-NCAH phenotype is determined by the less severe CYP21A2 mutation with the highest residual 21OH enzymatic activity.

### Genotyping for
- genetic counseling purposes
- confirmation of diagnosis
  - (NCAH/CAH boundary)
**Homozygote**

**Heterozygote Carriers**

- 21-OHdmild- 21-OHnormal
- 21-OHdsevere-21-OHnormal

**NCAH**

- 21-OHdmild^1- 21-OHdmild^1—Homozygote
- 21-OHdmild^1- 21-OHdmild^2—Compound heterozygote
- 21-OHdmild- 21-OHdsevere

25-50% homozygous or compound heterozygous for two mild alleles

Remaining are compound heterozygous for a severe mutation on one allele

Nordenstrom A, EJE 2018
Carrier frequency for a classic CAH mutation
1/60 in general population

Heterozygosity for non-classic mutations (NCAH carrier frequency)
15% among Askenazi Jews
9.5% among Caucasians
200 unrelated Ashkenazi Jewish subjects vs 200 random US Caucasians  
Hannah-Shmouni F, Genets Med 2017

NCAH frequency
1/1000-1/2000 births in Caucasians (reports upto 1/200)
1-2% in certain ethnic groups (Askenazi Jews)

Nordenstrom A, EJE 2018
<table>
<thead>
<tr>
<th>Country</th>
<th>Total # of Women</th>
<th># NCAH (%)</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (NE)</td>
<td>22*</td>
<td>2 (9%)</td>
<td>Emans et al., 1983 [8]</td>
</tr>
<tr>
<td>USA (NE)</td>
<td>139</td>
<td>2 (1.4%)</td>
<td>Cobin et al., 1985 [9]</td>
</tr>
<tr>
<td>USA (NE)</td>
<td>164</td>
<td>4 (2.4%)</td>
<td>Azziz and Zacur, 1989 [10]</td>
</tr>
<tr>
<td>USA (SE)</td>
<td>86</td>
<td>2 (2.3%)</td>
<td>Azziz et al., 1993 [11]</td>
</tr>
<tr>
<td>USA (SW)</td>
<td>83</td>
<td>1 (1.2%)</td>
<td>Chetkowskii et al., 1984 [12]</td>
</tr>
<tr>
<td>USA (SE)</td>
<td>873</td>
<td>18 (1.6%)</td>
<td>Azziz et al., 2004 [13]</td>
</tr>
<tr>
<td>Canada</td>
<td>72</td>
<td>4 (5.5%)</td>
<td>Innanen and Vale, 1990 [14]</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>100</td>
<td>1 (1.0%)</td>
<td>Romaguera et al., 2000 [15]</td>
</tr>
<tr>
<td>Ireland</td>
<td>96</td>
<td>6 (6.2%)</td>
<td>McLaughlin et al., 1990 [16]</td>
</tr>
<tr>
<td>England</td>
<td>50</td>
<td>1 (2.0%)</td>
<td>Turner et al., 1992 [17]</td>
</tr>
<tr>
<td>France</td>
<td>400</td>
<td>24 (6.0%)</td>
<td>Kuttenn et al., 1985 [18]</td>
</tr>
<tr>
<td>France</td>
<td>69</td>
<td>16 (23%)</td>
<td>Blanche et al., 1997 [19]</td>
</tr>
<tr>
<td>Portugal</td>
<td>129</td>
<td>23 (17.8%)</td>
<td>Pall et al., (in press) [20]</td>
</tr>
<tr>
<td>Italy (South)</td>
<td>372</td>
<td>14 (4.0%)</td>
<td>Carmina et al., 1987 [21]</td>
</tr>
<tr>
<td>Italy (North)</td>
<td>85</td>
<td>1 (1.1%)</td>
<td>Motta et al., 1988 [22]</td>
</tr>
<tr>
<td>Italy (Palermo)</td>
<td>950</td>
<td>41 (4.5%)</td>
<td>Carmina et al., 2006 [23]</td>
</tr>
<tr>
<td>Spain</td>
<td>270</td>
<td>6 (2.2%)</td>
<td>Escobar-Morreale et al., 2008 [24]</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>298</td>
<td>8 (2.7%)</td>
<td>Fanta et al., 2008 [25]</td>
</tr>
<tr>
<td>Greece</td>
<td>107</td>
<td>10 (9.3%)</td>
<td>Trakakis et al., 2008 [26]</td>
</tr>
<tr>
<td>Turkey (Ankara)</td>
<td>32*</td>
<td>1 (3%)</td>
<td>Akinci et al., 1992 [27]</td>
</tr>
<tr>
<td>Turkey (Istanbul)</td>
<td>61</td>
<td>20 (33%)</td>
<td>Yarman et al., 2004 [28]</td>
</tr>
<tr>
<td>Turkey (Kayseri)</td>
<td>285</td>
<td>6 (2.1%)</td>
<td>Unluhizarci et al., 2010 [29]</td>
</tr>
<tr>
<td>Turkey (Central Anatolia)</td>
<td>63</td>
<td>6 (9.5%)</td>
<td>Kamel et al., 2003 [30]</td>
</tr>
<tr>
<td>Israel</td>
<td>170</td>
<td>14 (8.2%)</td>
<td>Eldar-Geva et al., 1990 [31]</td>
</tr>
<tr>
<td>India</td>
<td>60</td>
<td>3 (8.3%)</td>
<td>Mithal et al., 1988 [32]</td>
</tr>
<tr>
<td>India</td>
<td>63</td>
<td>3 (5.7%)</td>
<td>Khandekar et al., 1990 [33]</td>
</tr>
</tbody>
</table>

*adolescent girls.

Worldwide prevalence among hyperandrogenic women is 4.2%

Witchel SF, Int J Ped Endocrinol 2010; Carmina E, Human Reprod 2017
The phenotype of NCAH patients is classically determined by the less severe \textit{CYP21A2} mutation with the highest residual 21OH enzymatic activity.
<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Girls</th>
<th>Women</th>
<th>Boys</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature adrenarche</td>
<td>Hirsutism</td>
<td>Premature adrenarche</td>
<td>Family screening</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>Menstrual cycle disorders</td>
<td>Family screening</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td>Increased Growth velocity</td>
<td>Acne</td>
<td>Increased Growth velocity</td>
<td>Adrenal incidentaloma</td>
</tr>
<tr>
<td></td>
<td>Family screening</td>
<td>Infertility</td>
<td>Acne</td>
<td>Infertility</td>
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<tr>
<td></td>
<td>Clitoromegaly</td>
<td>Family screening</td>
<td>Gynecomastia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clitoromegaly</td>
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<td>Adrenal incidentaloma</td>
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<tr>
<td></td>
<td></td>
<td>Short stature</td>
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</tbody>
</table>
Clinical and Molecular Characterization of a Cohort of 161 Unrelated Women with Nonclassical Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency and 330 Family Members

Maud Bidet, Christine Bellanné-Chantelot, Marie-Béatrice Galand-Portier, Véronique Tardy, Line Billaud, Kathleen Laborde, Christiane Coussieu, Yves Morel, Christelle Vaury, Jean-Louis Golmard, Aurélie Chakhtoura, Etienne Mornet, Zeina Kuttenn, Irene Mowszowicz, Anne Bachelot, Philippe Touraine, and Frédérique Kuttenn

<table>
<thead>
<tr>
<th>Group</th>
<th>Genotypes</th>
<th>n</th>
<th>%</th>
<th>Total %</th>
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<tr>
<td>Group A: mild/mild (n = 43)</td>
<td>V281L/V281L</td>
<td>31</td>
<td>25</td>
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<td></td>
<td>V281L/P453S</td>
<td>9</td>
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<td>V281L/P30L</td>
<td>2</td>
<td>1.6</td>
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<td></td>
<td>P453S[V281L;P453S]</td>
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<td>Group B: mild/severe (n = 75)</td>
<td>V281L/V52-13A/C&gt;G</td>
<td>22</td>
<td>17.7</td>
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<td>V281L/large deletion</td>
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<td>V281L/I172N</td>
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<td>V281L/Q318X</td>
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<td>V281L/R483P</td>
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<td>V281L/S’gene conversion</td>
<td>4</td>
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<td>V281L/R356W</td>
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<td>V281L/W19X</td>
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<tr>
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<td>V281L/G110fs</td>
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<tr>
<td></td>
<td>V281L/L307fs</td>
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<tr>
<td></td>
<td>V281L/R408C</td>
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<tr>
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<td>V281L/complex rearrangement</td>
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<td>V281L[I172N;V281L]</td>
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<tr>
<td></td>
<td>P453S[V52-13A/C&gt;G]</td>
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<td>P453S[V318X;R356W]</td>
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<td>0.8</td>
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<tr>
<td></td>
<td>P30L/I172N</td>
<td>4</td>
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<tr>
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<td>P30L/V52-13A/C&gt;G</td>
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<td>1.6</td>
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<tr>
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<td>P30L/[V281L;R483Q]</td>
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<tr>
<td></td>
<td>R435C/Q318X</td>
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<td>0.8</td>
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<tr>
<td>Group C: severe/severe (n = 4)</td>
<td>IV52-13A/C&gt;G/IV52-13A/C&gt;G</td>
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<td>0.8</td>
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</tr>
<tr>
<td></td>
<td>I172N/I172N</td>
<td>1</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q318X/G3755</td>
<td>1</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S’ gene conversion/large deletion</td>
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<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Novel genotype</td>
<td>V281L/S460_P465del</td>
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<td>0.8</td>
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<tr>
<td>Only one mutation found</td>
<td>Q318X</td>
<td>1</td>
<td>0.8</td>
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60.5%
<table>
<thead>
<tr>
<th></th>
<th>A mild/mild (n = 43)</th>
<th>B mild/severe (n = 75)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis (yr)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>23.2 ± 8</td>
<td>21.2 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22.0 (6–46)</td>
<td>21.5 (5–42)</td>
<td></td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.4 ± 1.5</td>
<td>12.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12.0 (10–17)</td>
<td>12.0 (8.5–16)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
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<td></td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>162.7 ± 4.9</td>
<td>161.4 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>163 (153–173)</td>
<td>161 (147–175)</td>
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<tr>
<td>Hirsutism</td>
<td></td>
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<tr>
<td></td>
<td>78.0% (32/41)</td>
<td>73.9% (54/73)</td>
<td>NS</td>
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<tr>
<td>Premature pubarche</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.3% (3/41)</td>
<td>11.8% (8/68)</td>
<td>NS</td>
</tr>
<tr>
<td>Cycles</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lary amenorrhea</td>
<td>5.1% (2/39)</td>
<td>16.2% (12/74)</td>
<td>NS</td>
</tr>
<tr>
<td>Lapar amenorrhea</td>
<td>10.3% (4/39)</td>
<td>2.9% (2/68)</td>
<td>NS</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>58.9% (23/39)</td>
<td>47.0% (32/68)</td>
<td>NS</td>
</tr>
<tr>
<td>Regular</td>
<td>25.6% (10/39)</td>
<td>38.2% (26/68)</td>
<td>NS</td>
</tr>
<tr>
<td>17 OHP (ng/ml)</td>
<td></td>
<td></td>
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<tr>
<td>Basal</td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>6.9 ± 7.2</td>
<td>15.6 ± 14.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.5 (1–41)</td>
<td>11.0 (0.61–88)</td>
<td></td>
</tr>
<tr>
<td>After ACTH</td>
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<tr>
<td>Mean ± SD</td>
<td>24.8 ± 12.4</td>
<td>42.1 ± 20.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>25.5 (11–59)</td>
<td>45.0 (11.6–108)</td>
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<tr>
<td>T (ng/ml)</td>
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<tr>
<td>Mean ± SD</td>
<td>0.7 ± 0.3</td>
<td>0.96 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.6 (0.2–1.5)</td>
<td>0.8 (0.26–2.7)</td>
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<tr>
<td>AT4 (ng/ml)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>3.5 ± 1.5</td>
<td>4.9 ± 2.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.1 (1.2–9.2)</td>
<td>4.65 (1.2–14.7)</td>
<td></td>
</tr>
</tbody>
</table>
NCAH-Severe mutation carriers on one allele:
- Have higher androgen levels
- May have earlier onset of symptoms - severe clinical presentation

ACTH-stimulated 17OHP
- SW >1000 ng/ml
- SV 100-300 ng/ml
- NCAH 15-100 ng/ml
Adrenal androgen excess could be treated either by:

- Suppressing adrenal androgen production with glucocorticoids

- Blocking the androgen effects on their receptors with anti-androgens
  Cyproterone acetate (CPA)

  **30 ptsn with hirsutism CPA vs Hydrocortisone (54% vs 24%)**
  Spritzer P, JCE&M 1990

  Spironolactone  Flutamide  Finasteride

  **Anti-mineralocorticoid action  **Risk of impaired virilization of external genitalia of a male fetus

- Suppressing ovarian androgen production
  Estrogen–progestin combination preparations  (40-60% androgen reduction-*SHBG)
  GnRH agonists

Carmina E, Human Reprod 2017
Case 2
28 years old female admitted with the complaint of infertility

Medical History
Pubarche at the age 7 and she was a tall child
She had menarche at the age of 13y and reported irregular menses if she did not take her OC pills (first prescribed by her family physician)
At the age of 16, she noticed facial hair and cystic acne refractory to antibiotics
She was diagnosed to have NCAH due to 21OHd
She was diagnosed as a compound heterozygote for a mild (V281L) and severe (intron 2G) mutation carrier in the CYP21A2 gene
Impact of NCAH on female fertility

Hyperandrogenemia-disturbed HPO axis
Oligo/anovulation
PCOS-like phenotype

Pregnancy rates at 1 year; NCAH vs controls ----67% and 76%  Bidet M, JCE&M 2010
Mechanisms of subfertility in NCAH

-Tonic oversecretion of androgens-aromatized to estrogens results in loss of gonadotropin cyclicity--augmentation of pituitary sensitivity to LHRH and increase LH release-mimicking PCOS-------anovulation or dysovulation

-Ovarian hyperandrogenism with secondary PCOS

-Increased adrenal progesterone production may have an inhibitory effect by:
  - Altering the rhythm and amplitude of GnRH pulses
  - Interfering with ovulation-endometrial development-implantation-poor nidation capacity
  - Diminished sperm-tubal motility and thickening of cervical mucus

-Adrenal androgens may directly inhibit folliculogenesis (a negative effect on aromatase activity in granulosa cells?)

-Direct effects of elevated androgens on GnRH pulse generator itself (?)

### Factors affecting fertility in women with CAH and their age-matched controls--Outcome of pregnancies

<table>
<thead>
<tr>
<th></th>
<th>CAH (n= 62)</th>
<th>Controls (n= 62)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>30 (18–63)</td>
<td>31 (19–63)</td>
<td>NS</td>
</tr>
<tr>
<td>Menarche age, years (range)</td>
<td>13.1 (8–20)</td>
<td>12.8 (10–16)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy attempt (n )</td>
<td>19</td>
<td>41</td>
<td>&lt;0.0098</td>
</tr>
<tr>
<td>Never pregnant n(%)</td>
<td>46 (74%)</td>
<td>21 (34%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Age first pregnancy, years (range)</td>
<td>30.0 (21–39)</td>
<td>27.7 (19–42)</td>
<td>NS</td>
</tr>
<tr>
<td>Irregular menstruation n (%)</td>
<td>11/39 (28%)</td>
<td>9/32 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ever pregnant (n)</td>
<td>16</td>
<td>41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total number of pregnancies (n)</td>
<td>31</td>
<td>76</td>
<td>&lt;0.0001</td>
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<tr>
<td>Term pregnancies (n)</td>
<td>25</td>
<td>54</td>
<td>&lt;0.0056</td>
</tr>
<tr>
<td># of children</td>
<td>25</td>
<td>54</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Pre-eclampsia n (%)</td>
<td>0/25 (0)</td>
<td>2/54 (3.7%)</td>
<td>NS</td>
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<tr>
<td>Caesarean section n (%)</td>
<td>21/25 (84%)</td>
<td>5/54 (9%)</td>
<td>&lt;0.001</td>
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### Mutation

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<tr>
<th>Mutation</th>
<th>Classical/Classical</th>
<th>I2splice</th>
<th>SV</th>
<th>NCAH</th>
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<tbody>
<tr>
<td>#</td>
<td>14</td>
<td>15</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td># with children (%)</td>
<td>0 (0)</td>
<td>2 (13%)</td>
<td>9 (33%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

Pregnancy and delivery rates------lower CAH women
Severity of 21-OH-mutation correlated with low live births
Sexual Orientation in Women with CAH and NCAH

Sexual Behavior Assessment Schedule

Bisexual/Homosexual partner experience
- Increased in all
- Not correlated with the severity of genotype

<table>
<thead>
<tr>
<th></th>
<th>COS (n = 22)</th>
<th>NC (n = 80)</th>
<th>SV (n = 21)</th>
<th>SW (n = 38)</th>
<th>p (ANOVA)</th>
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</thead>
<tbody>
<tr>
<td>Same-sex sex partners</td>
<td>0.0 (0.0)</td>
<td>0.2 (0.45)</td>
<td>0.1 (0.2)</td>
<td>0.5 (1.5)</td>
<td>.037</td>
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<tr>
<td>None</td>
<td>22</td>
<td>71</td>
<td>20</td>
<td>32</td>
<td></td>
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</tbody>
</table>

Mild androgen excess NCAH fetuses is insufficient to affect the sexual differentiation of the genitalia, but is sufficient to affect the sexual differentiation of the brain.  

Meyer-Bahlburg HFL, Arch Sex Behav 2008
NCAH-FERTILITY TREATMENT OPTIONS

- Glucocorticoids
- Clomiphene Citrate
- Gonadothropins (rarely)
- Mineralocorticoids (rarely)
Fertility in women with late-onset adrenal hyperplasia due to 21OHD

53 NCAH females (20 desiring pregnancy)
38 pregnancies
18 spontaneous/ 20 with treatment

16 desiring pregnancy-FU with Hydro only

For therapeutic efficacy

Clinical criteria
- Regular cycles
- Diphasic basal body temperature curve

Biological criteria
- Fall in plasma T and A values to normal
### Clinical characteristics (n=190)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age at diagnosis (yr)</td>
<td>23.6±9.7</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>12.5±1.6</td>
</tr>
<tr>
<td>Premature pubarche (%)</td>
<td>10</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24±4.6</td>
</tr>
<tr>
<td>Hirsutism (%)</td>
<td>71.8</td>
</tr>
<tr>
<td>Primary amenorrhea (%)</td>
<td>8.2</td>
</tr>
<tr>
<td>Secondary amenorrhea (%)</td>
<td>4.4</td>
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<tr>
<td>Oligomenorrhea (%)</td>
<td>46.2</td>
</tr>
<tr>
<td>Regular menstrual cycles (%)</td>
<td>41.2</td>
</tr>
<tr>
<td>Infertility (%)</td>
<td>11</td>
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</table>

### Pregnancy occurrence and outcome according to glucocorticoid treatment (Tt)

<table>
<thead>
<tr>
<th></th>
<th>Pregnancies without GC (n=110)</th>
<th>Pregnancies with GC (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spontaneous (n)</td>
<td>With ovulation inducers (n)</td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>107</td>
<td>3</td>
</tr>
<tr>
<td>*Miscarriages</td>
<td>27 (25.2%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>(26.3%)</em></td>
<td><em>(6.5%)</em></td>
</tr>
</tbody>
</table>

*Poor quality of ovulation and/or inadequate corpus luteum

*Risk of miscarriage without GC higher (odds ratio: 4.5, 95% confidence interval: 1.4–14.2)

Bidet M, JCE&M 2010
n=75 NCAH women with 187 pregnancies
(84% homozygous for V281L mutation)

**Time to conceive (months)**

n=45 without GC vs n=94 with GC
4.0 ± 7 mo vs 3.3 ± 3 mo (p=0.43)

17 pregnancies with GC (*)
10.2 ± 11.4 mo vs 3.3 ± 3.4 mo
(p = .02)

135 pregnancies (72%)-live births
(77% in healthy population)

---

Eyal O, Clin Endocrinol 2017
Glucocorticoid treatment
- Enables conceiving
  follicular-phase progesterone-0.6 ng/mL = 2 nmol/L
early morning 17OHP<8.0ng/ml and andostenodione -N
- Prevents early pregnancy loss
- Improves pregnancy outcomes

Hydrocortisone 20-25mg/day
Prednisone 2.5-5mg/day

Dexamethasone ?
- Not metabolized by placental 11B-hydroxysteroid dehydrogenase type 2

Moran C, JCE&M 2006; Casteras A, Clin Endocrinol 2009; Bidet M, JCE&M 2010
Reproductive Outcome of Women with 21-Hydroxylase-Deficient Nonclassic Adrenal Adrenal Hyperplasia


Multicenter study 9 Centers 331 NCAH
n=101 (203 pregnancies)
Infertility—21.8%
No difference in Ectopic Pregnancy, Preterm Birth, Stillbirths, Twins/Multiple Pregnancies
203 pregnancies

138 pregnancies (68%)
Before NCAH diagnosis

138 pregnancies (68%)
Before NCAH diagnosis

65 pregnancies (32%)
After NCAH diagnosis

65 pregnancies (32%)
After NCAH diagnosis

35 Miscarriages (25.4%)

35 Miscarriages (25.4%)

4 Miscarriages (6.2%)

4 Miscarriages (6.2%)

Miscarriage rate 19.2%
203 pregnancies

138 pregnancies (68%)
Before NCAH diagnosis
- 94 (68%) Spontaneous
- 5 (3.6%) GC
- 4 (2.9%) CC
- 1 (0.7%) GC+CC
- 1 (0.7%) GC+Menotropin
- 33 (23.9%) No data

65 pregnancies (32%)
After NCAH diagnosis
- 16 (24.6%) Spontaneous
- 35 (53.8%) GC
- 5 (7.7%) CC
- 6 (9.2%) GC+CC
- 1 (1.5%) GC+Menotropin
- 1 (1.5%) CC+Menotropin

Clomiphene citrate (CC)
Glucocorticoids (GC)

Moran C, JCE&M 2006
Treatment of NCAH

- In asymptomatic nonpregnant NCAH individuals, GC treatment is not recommended

- In adult women with NCAH who have infertility or have a history of previous miscarriage, GC treatment is suggested

  ***Dex is not the GC of choice

  ***Reverse GC regime—Only for short periods of time

  ***Goal= Normal Menses, Biphasic basal body temperature, Normal T&A

  ***P30L/null genotypes or phenotypes with classic/non-classic boundary—Cases with recurrent miscarriages may benefit from low GC throughout pregnancy

  ***Risk of adrenal crises for NCAH cases on GC !!!!

Speiser PW, JCE&M 2018
Probability of a NCAH woman having a baby with classical CAH is 1/480

1/60-carrier for a severe mutant allele
½ of NCAH carry a severe mutation
¼ for OR transmission

1/60 X 1/2 X 1/4 = 1/480 (% 0.002)
Reproductive Outcome of Women with 21-Hydroxylase-Deficient Nonclassic Adrenal Hyperplasia


162 live births (51.2% female, 48.8% male)

- 4 (2.5%) Classical CAH
  - 3 males SW
  - 1 female SV

- 24 (14.8%) NCAH
  - 13 females
  - 11 males

Risk of a child affected with
- CAH------2.5% (predicted rate-1/480--0.002%)
- NCAH ---14.8% (predicted rate-1/32—3.1%)

The impact of ethnicity is obvious---intermarry within same ethnic population
Infertile female NCAH with mild/severe mutation + Male Partner-severe mutation carrier

Can DEXA be preferred?

- Prednisolone
- Hydrocortisone
- Dexamethasone

- Given for suppressing maternal androgens
- Not for protecting fetus from maternal androgens

PRENATAL THERAPY

- Not a substrate for plasental 11-B HSD-2
- Transferred to fetus and suppresses fetal androgen production
GENITAL DIFFERENTIATION

Androgen excess during the critical period of 7–12 weeks gestation can lead to varying degrees of masculinization of the female fetus:

labial hypertrophy and clitoromegaly ----complete labioscrotal fusion and penile urethra formation


*Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod Update 2004;10:469-85

**PRENATAL DEXA**

Success rate for ameliorating genital virilization-----80-85%

Miller WL, Am J Obst 2013
Prenatal Dexamethasone Treatment

20 mcg/kg/maternal body weight (in 2-3 divided doses) (without exceeding 1.5 mg/day)

(must be initiated at latest 7th WG or 9th week of amenorrhea)

This dose exceeds the physiological GC needs

>6 times of mother >60 times of fetus

Dexa—Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
POTENTIAL ADVERSE EFFECTS OF DEXA

Fetal safety (*Developmental origins of adult disease*)

- Teratogenicity
  - Increased risks of orofacial clefts
- Animal studies
  - Renal dysgenesis
  - Reduced pancreatic β cell numbers
  - Impaired glucose tolerance
  - Increased systolic and diastolic blood pressure
  - Altered hepatic programming-increased lipid accumulation
  - Impaired thyroid development with low follicular and C cell numbers
  - Reduced germ cell density via increasing apoptosis in oogonia (in vitro)
  - Alterations in DNA methylation-permanently affecting expression of genes in carbohydrate homeostasis and programming of HPA axis
- Low birth weight (about 400gr lower)
Prenatal dexamethasone use for CAH (4 observational studies)

325 CAH pregnancies with DEXA

Fernandez-Balsells MM, Clin Endocrinol 2010
Prenatal DEX therapy is still experimental---Not routinely recommended

Pregnant women at risk for carrying a fetus affected with classical CAH

- History of giving birth to a baby with CAH and planning pregnancy with the same partner

Known heterozygote carriers for severe mutations (both father and mother)*

Only protocols approved by Institutional Review Boards at experienced centers are recommended

**Massively parallel sequencing (MPS) of cell-free fetal DNA in maternal plasma  New MI, JCEM 2014

**Fetal sex determination in the maternal serum (SRY test)  Tardy-Guidollet V, JCEM 2014

**Preimplantation genetic testing (PGT); selecting only genetically normal embryos for transfer  Chan J, Stem Cells 2005
How to follow a NCAH pnt with GC during pregnancy?

- Increase GC dose (?)
  - Increased adrenal steroid production
  - Altered steroid clearance
  - Increase in sex hormone–binding globulin
  - Increase in placental aromatization (during the third trimester)

- Blood pressure control

- Gestational DM

- During labor and delivery, stress doses of GCs should be administered

**Maternal 17OHP is elevated in normal pregnancy-No use in monitoring GC tx**

Nordenstrom A, EJE 2018
THANK YOU FOR YOUR ATTENTION