The Medical Management of Gender Dysphoria using GnRHa; A review of the published evidence of the use GnRHa for gender dysphoria in adolescents

November 2024

Newcastle Ottawa Scale Assessment for Case controlled studies

No	Country Year	Reference	Selection (max 1 star per item)				Compatibility (max 2 stars per item)	Exposure			Rating
			Case Definition Adequate	Representative-ness of Cases	Selection of controls	Definition of controls	Comparability cases & controls on the basis of design or analysis	Assessment of Exposure	Same method of Ascertainment	Non-response rate	
10	**USA 2021**	**(Nokoff et al., 2021a)**	Cases selected from GIS. Diagnostic criteria not stated	Cases assumed to be representative of GD adolescents eligible for GnRHa	Cohort of children at same institution undergoing the same formal investigations	Cis-gender non exposed to GnRHa	Research conducted in the same institution undergoing the same investigations. Matched for age.	Medical / trial records	Same investigations reported.	Non-response not stated.	Good
15	**N'lands 2015**	**(Staphorsius. et al., 2015)**	Cases selected from GIS. Diagnosis based on DSM 4/5	Cases assumed to representative of GD individuals eligible for GnRHa.	GD individuals matched for age Tanner stage and sex.	1. Cisgender controls 2. Untreated GD	1. Control group of cis gender friends of cases 2. Treated and untreated GD Analysis adjusted for key variables.	Medical records	DEXA and MRI	30 excluded but breakdown not provided.	Good

No	Country Year	Reference	Selection (max 1 star per item)				Compatibility (max 2 stars per item)	Exposure			Rating
			Case Definition Adequate	Representative-ness of Cases	Selection of controls	Definition of controls	Comparability cases & controls on the basis of design or analysis	Assessment of Exposure	Same method of Ascertainment	Non-response rate	
17	**N'lands 2020**	**(van de Grift et al., 2020)**	Cases selected from GIS. Diagnosis based on DSM 4/5	Cases assumed to be representative of GD individuals eligible for GnRHa	Same GIS clinic matched for age, CSH therapy and requesting surgery	GnRHa therapy excluded.	By design: Individuals enrolled in GIS clinic. By Analysis: Age: Tanner status, Gender,	Medical records	Same investigations reported	Eligible cases = 316. Included for analysis = 200.	Good

USA = United States of America, N'lands = Netherlands, GIS = Gender Identity Service, GD = gender Dysphoria, GnRHa = gonadotrophin releasing hormone analouge, DSM-4/5 = Diagnostic and Statistical manual, version 4 or 5, DEXA – Dual Emission X-ray Analysis.

NOS Criteria Definitions for Case Control Studies

Selection

Case definition adequate

- Case definition of gender dysphoric individuals receiving GnRHa accepted as accurate on the basis of individuals being managed through GIS with diagnostic criteria. GnRHa administration occurs though injections or implants which reduces non-compliance due to self-medication risks. Duration of therapy for executive function, and cardiometabolic outcomes and surgical options acceptable based on limited information.

Representativeness of cases

- Truly representative of the average adolescent with GD in Gender Identity Service Clinics for GnRHa. Diagnosis accepted if recognised method stated, or if the individual was managed through a specialist Gender Identity service. For the purpose of analysing medical complications of GnRHa, attendance through a publicly funded GIS clinic is accepted as being representative of individuals with GD receiving GnRHa. This assumption has not been applied for the analysis of psychosocial outcomes.

Selection of controls

- Controls selected through the same GIS or for non-GD controls through the same institution, undergoing the same investigation

Definition of controls

- Unexposed to GnRHa or without GD

Comparability

Comparability of cases and controls on the basis of design or analysis

- Study controls for primary outcome
- Study controls for secondary outcomes

Exposure

Ascertainment of Exposure

- Medical Notes

Non-response Rate

- Same for both groups.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Newcastle Ottawa Scale Assessment for Bone Mineral Density Cohort Studies

Study No	Country / Year	Reference	Selection of Study Groups				Comparability of Cohorts	Ascertainment of Exposure / Outcome			Comment /Rating
			Cases Representa-tive	Selection of non-exposed cohort	Ascertainment of Exposure	Outcome not present at start of study		Assessment of Outcome	Follow-up duration	Follow-up Cohort	
2	**N'lands 2023**	**(Boogers et al., 2023)**	Retrospective GIS cohort with protocol	National Health and Nutrition Examination Surveys	GnRHa prescribed through GIS	Complete BMD-Z scores prior to GnRHa not provided.	BMD-Z score data not provided. AMAB only included in study	BMD-Z score data not provided.	All > 1 year. Mean (SD) > 2 years (0.7)	157 eligible participants, 87 included. Excluded cohort not analysed.	**Poor** Numerical BMD-Z-scores not provided Primary outcomes after GAHT
3	**UK 2021**	**(Carmichael et al., 2021)**	Prospective GIS cohort with protocol	Reference range for HABMD-Z-scores not provided	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol to 3 years.	BMD-z scores not categorised by sex assigned at birth.	BMD z-scores from medical records	Longest follow up provided up to three years.	Prospective. 44 sequential cases. 1/44 lost at 12 months.	**Poor** Lack of categorisation and reference range description.
6	**UK 2019**	**(Joseph et al., 2019)**	Retrospective GIS cohort with protocol	Reference range based on published UK norms for Caucasian subjects	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol to 3 years.	BMD-Z scores provided AMAB & AFAB analysed separately. Narrow age range 12 – 14 years	BMD z-scores from medical records	All > 1 year up to 3 years	All eligible individuals enrolled during study period included	**Good**
8	**N'Lands 2015**	**(Klink. et al., 2015)**	Retrospective GIS cohort with protocol	BMD z-score National Health and Nutrition Examination Surveys BAMD z-score published reference	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol to initiation of GAHT till age 18	Broad age range 11.4 – 18.3 years	BMD z-scores from medical records	GnRHa treatment median 1.3 years range 0.5 – 3.8 years	Follow-up data not provided. Primary endpoint 22 years	**Good** Purpose of study to assess BMD after GnRHa and GAHT therapy at age 22 years.

9	**Canada 2021**	**(Navabi et al., 2021)**	Retrospective GIS cohort with protocol	BMD reference range based on published data	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol to 3 years.	Age, Tanner status, bone age not reported for GnRHa subgroup. AMAB & AFAB analysed separately.	BMD z-scores from medical records	GnRHa treatment median or range not provided for GnRHa subgroup.	Eligible = 198 Included = 172 FU = 87%	**Poor** GnRHa cohort a sub-analysis of larger cohort.
13	**N'lands 2020**	**(Schagen et al., 2020)**	Prospective GIS cohort with protocol	BMD z-score National Health and Nutrition Examination Surveys BAMD z-score published reference	GnRHa prescribed through GIS	Prospective study with baseline BMD data.	Analysis by early or late puberty based on Tanner stage.	BMD z-scores from medical records	GnRHa duration mean (SD) 2.0 ± 0.94	127 cases enrolled. 121 completed protocol.	**Good**
16	**N'lands 2019**	**(Stoffers et al., 2019)**	Prospective GIS cohort with protocol	BMD z-score National Health and Nutrition Examination Surveys BAMD z-score published reference	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol	Broad age range, pubertal development. AFAB only included in study	BMD z-scores from medical records	All GnRHa > 6 mo. GnRHa duration median (range) 8 (3-39)	64 eligible, 62 included in analysis	**Poor**
19	**N'Lands 2017**	**(Vlot et al., 2017)**	Retrospective cohort with GIS protocol	Published reference range	GnRHa prescribed through GIS	Longitudinal study with yearly assessment protocol	Separate analysis for young and older individuals based on bone age. Small numbers (range 5 – 23) in each group.	BMD z-scores from medical records	Duration of GnRHa not provided. > 1 year in median age between baseline and initiation of GAHT.	Eligible individuals = 215 Included = 112 No analysis of excluded cases.	**Good**

BMD = Bone Mineral Density, BMAD, Bone mineral areal density, DSM-4/5 = Diagnostic and Statistical manual, version 4 or 5, DEXA – Dual Emission X-ray Analysis, GIS = Gender Identity Service, GD = gender Dysphoria, GnRHa = gonadotrophin releasing hormone agonist, N'lands = Netherlands, UK = United Kingdom, , USA = United States of America.

NOS Criteria definitions: BMD

Selection

Representativeness of cases

- Cohort considered representative of adolescents diagnosed with GD eligible for GnRHa if investigations undertaken as part of a specific protocol through a recognised GIS

Description of non-exposed cohort

- Drawn from same cohort of adolescents with GD not treated with GnRHa an accepted control
- Comparison to validated published population reference ranges.

Ascertainment of Exposure

- Medical record of having received GnRHa.

Demonstration that outcome of interest was not present at start of study

- For longitudinal studies analysis prior to and after initiation of GnRHa treatment
- For cross sectional studies comparisons to validated published population reference ranges

Comparability

Comparability of cohorts

- For BMD studies, BMD-z scores or similar categorised by sex assigned at birth required
- Adjusted by age, Tanner status, bone age.

Outcome

Assessment of Outcome

- Independent Blind assessment

- Record linkage for data extracted from medical notes

Adequate follow-up duration

- Minimum of 6 months for BMD studies.

Adequate follow up of cohorts

- All subjects accounted for
- Small proportion (<15%) unlikely to influence results

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)
Good quality: 3 or 4 stars in selection domain **AND** 1 or 2 stars in comparability domain **AND** 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain **AND** 1 or 2 stars in comparability domain **AND** 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Newcastle Ottawa Scale Assessment for Cardiometabolic Cohort Studies

Study No	Country Year	Reference	Selection of Study Groups				Comparability of Cohorts	Ascertainment of Exposure / Outcome			Comment / Rating
			Cases Representative	Selection of non-exposed cohort	Ascertainment of Exposure	Outcome not present at start of study		Assesment of Outcome	Follow-up duration	Follow-up Cohort	
7	**N'Lands 2019**	**(Klaver et al., 2020)**	Retrospective cohort with GIS protocol	Published relevant reference ranges	GnRHa prescribed through GIS	Longtitudinal study with baseline data.	AMAB and AFAB analysed separately Linear mixed model regression with analaysis for missing values.	Data from medical records	Difference in mean duration of GnHRa monotherapy 1.8 yrs AMAB and 1.7 yrs AFAB.	Not provided	**Good**
11	**Israel 2020**	**(Perl et al., 2021)**	Retrospective cohort with GIS protocol	Published relevant reference ranges	GnRHa prescribed through GIS	Longtitudinal study protocol with baseline data.	Study only included AFAB adolescents.	Medical Records	All treated for > 2 months.	Small number of cases n= 15 3 missing data (20%)	**Poor** **Time required for BP alterations unknown.**
12	**N'lands 2016**	**(Schagen et al., 2016)**	Retrospective cohort with GIS protocol	Reference range for creatinine not provided	GnRHa prescribed through GIS	Longtitudinal study protocol with baseline data.	AMAB and AFAB analysed separately. Broad age range (11.6 – 17.9 years)	Medical Records	All at 1 year.	AMAB 28/36 (78%) AFAB 29/41 (70%)	**Good**
16	**N'lands 2019**	**(Stoffers et al., 2019)**	Prospective GIS cohort with protocol	Reference range for Blood pressure not provided	GnRHa prescribed through GIS	Longtitudinal study with yearly assessment protocol	AFAB only included in study Broad age range, pubertal development. BP data during GnRHa unadjusted for age.	BP from medical records	All GnRHa > 6 mo. GnRHa duration median (range) 8 (3-39)	64 eligible, 62 included in analysis	**Poor** **Primary aim of study was BMD.**

NOS Criteria definitions: Cardiometabolic

Selection

Representativeness of cases

- Cohort considered representative of adolescents diagnosed with GD eligible for GnRHa if investigations undertaken as part of a specific protocol through a recognised GIS

Description of non-exposed cohort

- Drawn from same cohort of adolescents with GD not treated with GnRHa an accepted control
- Comparison to validated published population reference ranges.

Ascertainment of Exposure

- Medical record of having received GnRHa.

Demonstration that outcome of interest was not present at start of study

- For longitudinal studies analysis prior to and after initiation of GnRHa treatment
- For cross sectional studies comparisons to validated published population reference ranges

Comparability

Comparability of cohorts

- Cardiometabolic outcome z-scores or centiles categorised by sex assigned at birth required

Outcome

Assessment of Outcome

- Independent Blind assessment
- Record linkage for data extracted from medical notes

Adequate follow-up duration

- Minimum of 3/12 follow-up for cardiometabolic outcomes.

Adequate follow up of cohorts

- All subjects accounted for
- Small proportion (<15%) unlikely to influence results

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

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November 2024
HP 9067