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Review

Anti-Müllerian hormone kinetics in pregnancy and post-partum: a systematic review

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KEY MESSAGE

By systematically reviewing the available evidence, this paper suggests that anti-Müllerian hormone (AMH) serum concentration declines during pregnancy and increases to pre-pregnancy concentrations following delivery. The exact physiological mechanism of this decline is still unknown. For this reason AMH should not be used for assessing ovarian reserve during pregnancy.

A B S T R A C T

The aim of this systematic review is to critically appraise the available evidence regarding the kinetics of anti-Müllerian hormone (AMH) during pregnancy and post-partum. A systematic literature search was conducted in MEDLINE, Embase, CENTRAL, Scopus and Web of Science on 14 December 2015, aiming to identify studies providing data on the serum concentration of AMH in women at various stages of gestation and post-partum. There was a total of 1719 participants across eight studies. Seven out of the eight studies reported a decline in serum AMH concentration with advancing gestational age. Further, all four of the studies that evaluated pre- and post-delivery AMH concentrations found that it increased in the post-partum period. This review demonstrated an association between reduced maternal serum AMH concentrations and advancing gestational age, with a subsequent post-partum increase in concentration. These findings suggest that AMH measurements in pregnant women, especially at later stages of pregnancy, should not be used to assess ovarian reserve. Additionally, further longitudinal research would be beneficial, to elucidate the pathophysiological mechanism through which this decline in serum AMH concentration is observed during pregnancy.

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Introduction

Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance, is a member of the TGF-ß family most commonly known for its role in the regression of Müllerian ducts during male fetal sex differentiation. In females, AMH is produced by small antral and pre-antral follicles, and has been shown to inhibit excess recruitment of primordial follicles through reducing responsiveness to FSH (Durlinger et al., 2002a, 2002b). Hence, AMH seems to function in the ovary as a paracrine factor, rather than having any systemic hormonal actions (Cook et al., 2000). AMH serum concentration has been shown to be correlated with the ovarian follicular pool, so it is considered to be a marker of ovarian reserve as well as a marker of ovarian follicular activity (de Vet et al., 2002; Kwee et al., 2008; van Rooij et al., 2002a).

In non-pregnant women, the kinetics of AMH have been well studied (Dewailly et al., 2014; Durlinger et al., 2002a; La Marca et al., 2013; Nelson et al., 2011; Overbeek et al., 2012; van Rooij et al., 2002b; Visser and Themmen, 2005). Importantly, AMH has been shown to reduce with increasing age consistent with its role as a marker of ovarian reserve (de Vet et al., 2002). AMH remains relatively stable throughout the menstrual cycle, with the fluctuations reported in some studies appearing to be of small amplitude (Dewailly et al., 2014; La Marca et al., 2009). Further, it has been suggested that younger women might have more significant changes in AMH concentrations throughout their menstrual cycle, whilst older women might have less variation and a lower mean AMH concentration (Sowers et al., 2010).

Serum AMH concentrations have been found to decrease during the long-term use of hormonal contraception, such as the oral contraceptive pill (Dewailly et al., 2014), and then increase significantly following the cessation of hormonal contraception (van den Berg et al., 2010).

Much less is known about the fluctuations of AMH in pregnancy. This is an important area for research because AMH might reflect follicular recruitment during pregnancy. The current evidence regarding AMH kinetics in pregnancy is conflicting, with some studies concluding that it remains stable throughout pregnancy (La Marca et al., 2005), whilst others have found that it is more dynamic (Nelson et al., 2010). Hence, the aim of this systematic review is to identify, summarize and critically appraise evidence regarding the kinetics of AMH during pregnancy and post-partum.

Materials and methods

Search strategy

A systematic literature search was conducted in MEDLINE, Embase, CENTRAL, Scopus and Web of Science on 14 December 2015 to identify publications relevant to the kinetics of serum AMH during pregnancy. The electronic search was performed using the keywords described in **Table 1**, which included 'AMH' and 'pregnancy' as well as synonyms and closely related words in the abstracts, titles and keywords (**Table 1**). No language or date limits were applied.

Selection of studies

Studies were considered eligible regardless of their design, providing they contained data on AMH at different stages of gestation, from the same or different women. Initially 2514 publications were retrieved by two of the reviewers (S.M. and C.V.) and subsequently their titles were examined to exclude irrelevant studies, resulting in 44 potentially eligible studies (**Figure 1**). The abstracts of these publications were examined, leading to 19 articles whose full text was scrutinised, resulting in the identification of eight studies capable of answering the research question. During this process, duplicate publications were excluded, with the most recent or comprehensive publication analysed.

In two out of eight studies the association between AMH and gestational age was specifically evaluated (Köninger et al., 2013; La Marca et al., 2005). In the remaining six studies the association of AMH with fetal aneuploidy (n = 2) (Li et al., 2010; Plante et al., 2010), gestational diabetes mellitus (n = 1) (Gerli et al., 2015), fetal sex (n = 1) (Santillan et al., 2012), pre-term birth (n = 1) (Stegmann et al., 2015) and maternal adiposity (n = 1) (Nelson et al., 2010) was examined. Some of these studies reported AMH data separately for case and control groups and these data have also been extracted separately, where available. More specifically, in the study by Stegmann et al. (2015) the cases group included women of white race who delivered

Table 1 – Search strategy used for identification of eligible studies during electronic search.

Search step	Query
1	AMH OR antimulleri* hormone OR anti?muller* hormone OR MIS OR mullerian inhibit* OR antimüllerian hormone OR anti-müllerian hormone
2	Pregnancy OR Gestation OR Pregnant OR Gravida OR delivery OR birth
3	1 and 2

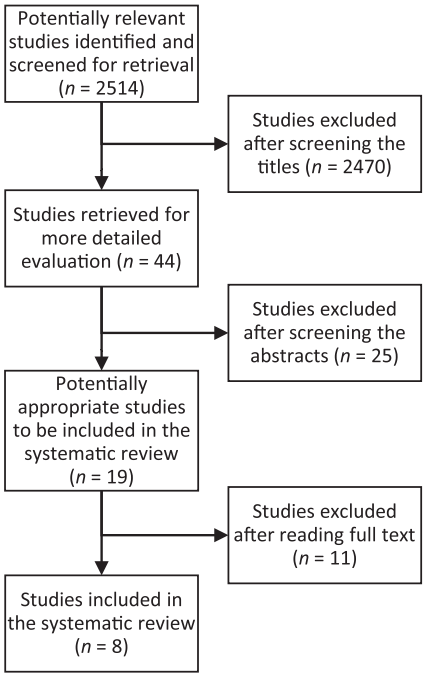

Figure 1 – Flow chart of study selection.

before term (*n* = 105) whilst the control group included women of white race who delivered at term (*n* = 95). In the study by Gerli et al. (2015) the cases group included women with gestational diabetes (*n* = 34) and the control group was comprised of women with healthy, singleton pregnancies, without gestational diabetes mellitus (*n* = 32). In the study by Li et al. (2010) the cases group included women with pregnancies affected by Down syndrome (*n* = 145) and the control group included women with pregnancies not affected by Down syndrome (*n* = 290).

Data extraction

Data extraction was performed by two of the reviewers (S.M. and C.V.) and the following information was recorded from each of the eligible studies: study, author, journal name, country of origin, study period, type of study, number of patients, number of measurements per patient, bias-reducing approach employed by authors, main research question addressed, population, mean age, gestational age at AMH measurement, AMH assay used, inter-assay and intra-assay coefficient of variation and mean or median serum AMH concentration in each trimester or post-partum.

Results

Eight studies fulfilled the inclusion criteria for the systematic review. Methodological and clinical characteristics of the eligible studies are listed in **Tables 2 and 3**. The studies were published between 2005 and 2015 and varied in size from 60 to 554 patients, with a total of 1719 patients across the studies. All data used in this systematic review were from pregnant women at various stages of gestation. Three of the studies originated in the USA, four in Europe and one in China.

There were four case-control studies (Gerli et al., 2015; Li et al., 2010; Plante et al., 2010; Stegmann et al., 2015), one of which was longitudinal in design (Gerli et al., 2015), one longitudinal cohort study (Nelson et al., 2010), two cross-sectional studies (La Marca et al., 2005; Santillan et al., 2012) and one study with a combination of cross-sectional and longitudinal components (Köninger et al., 2013). Three studies were designed prospectively (Gerli et al., 2015; La Marca et al., 2005; Nelson et al., 2010), four studies were retrospective (Li et al., 2010; Plante et al., 2010; Santillan et al., 2012; Stegmann et al., 2015), and one was a combination of prospective and retrospective components (Köninger et al., 2013) (**Table 2**). Gestational age at measurement varied across the studies, in accordance with their design.

Two of the studies were primarily aiming to determine the fluctuations of AMH in pregnancy (Köninger et al., 2013; La Marca et al., 2005), whilst the others were determining the association of AMH in pregnancy with pre-term birth (Stegmann et al., 2015), fetal sex (Santillan et al., 2012), gestational diabetes mellitus (Gerli et al., 2015), maternal adiposity (Nelson et al., 2010) or fetal aneuploidy (Li et al., 2010; Plante et al., 2010).

The DSL assay was used in one study (Nelson et al., 2010), the Immunotech Beckman-Coulter assay was used in one study (La Marca et al., 2005), and one study used both assays on their samples (AMHbc and AMHdsl) (Plante et al., 2010). One study used their own laboratory-developed assay (Stegmann et al., 2015). A further four studies used the most recently available AMH Gen II assay by Beckman-Coulter (Gerli et al., 2015; Köninger et al., 2013; Li et al., 2010; Santillan et al., 2012). Samples were frozen until time of measurement in three studies (Li et al., 2010; Plante et al., 2010; Stegmann et al., 2015) and five studies did not report whether their samples were stored prior to measurement (Gerli et al., 2015; Köninger et al., 2013; La Marca et al., 2005; Nelson et al., 2010; Santillan et al., 2012). Assay sensitivity or lowest limit of detection varied from 0.1 pmol/l to 0.7 pmol/l, although most had a value of 0.6–0.7 pmol/l (*n* = 5) (Gerli et al., 2015; Köninger et al., 2013; La Marca et al., 2005; Plante et al., 2010; Stegmann et al., 2015) and three studies did not report the assay sensitivity (Li et al., 2010; Nelson et al., 2010; Santillan et al., 2012). The inter-assay and intra-assay coefficients of variation ranged from 5% to 14.2% and 3% to 12.3%, respectively. Li et al. (2010) was the only study to report both intra-assay and inter-assay coefficients of variation greater than 10% (**Table 3**).

AMH kinetics during pregnancy

The results of the studies are presented in detail in **Table 4** and **Figures 2 and 3**.

First to second trimester changes

Seven of the studies identified in this systematic review provided evidence on the differences between AMH concentrations in the first and second trimesters of pregnancy. Six of the studies demonstrated a significant decrease in AMH during this gestational age, whilst one study demonstrated a non-significant increase in AMH concentrations (La Marca et al., 2005).

Two of the studies collected data longitudinally from the same cohort of patients, throughout their pregnancy (Köninger et al., 2013; Nelson et al., 2010). Nelson et al. (2010) found that circulating AMH reduced significantly with increased gestational age, with the median first trimester AMH concentrations declining by 2.6 pmol/l, from 11.2 pmol/l to 8.6 pmol/l, in the second trimester. Köninger et al. (2013) had a longitudinal cohort of 15 women in which they observed a non-significant decline of 2.64 pmol/l from a first trimester median AMH value of 19.49 pmol/l to a second trimester value of 16.85 pmol/l.

Köninger et al. (2013) also performed a larger, cross-sectional analysis of 450 patients which reported a significant decline from the first to the second trimester with median AMH measurements of 12.07 pmol/l and 5.71 pmol/l, respectively.

La Marca et al. (2005) performed a cross-sectional study, which found the mean AMH levels increased from 14.99 ± 4.00 pmol/l in the first trimester to 17.14 ± 4.57 pmol/l in the second trimester. This increase was not statistically significant.

Stegmann et al. (2015) performed a case-control study which, in the control group, produced mean AMH values of 25.7 ± 18.56 pmol/l in the first trimester and 21.42 ± 16.42 pmol/l in the second trimester of the pregnancies, which was a statistically significant decline. When considering AMH kinetics in the cases group (women with preterm birth) there was also a significant decrease in AMH concentrations (first trimester: 22.13 ± 17.14 pmol/l versus second trimester: 19.99 ± 14.99 pmol/l), however the decrease in AMH concentrations from the first to the second trimester was significantly greater in the control group. Similarly, Plante et al. (2010) performed a case-control study which found significant declines in AMH with increasing gestational

Table 2 – Methodological characteristics of included studies.

Study	Journal	Country of origin	Study period	Prospective or retrospective	Type of study	Number of patients	Number of measurements per patient	Controlling for confounders	Main research question addressed
Stegmann et al. (2015)	Fertility and Sterility	USA	2009–2010	Retrospective	Case-control	200 women	2 per patient	Prior history of pre-term birth, fetal gender, maternal age, maternal weight gain between first and second trimesters and smoking during pregnancy, gestational age at the time of blood sampling. Maternal race was limited to white.	Association of pre-term birth with AMH levels
Gerli et al. (2015)	Endocrine	Italy	August 2010 to June 2013	Prospective	Longitudinal case-control	66 women	3 per patient	Multivariate analysis controlling for the effect of female age, presence of gestational diabetes mellitus, BMI differences between measurements, newborn weight and placental weight	AMH concentrations in the third trimester of pregnancy and postnatally and their association with gestational diabetes mellitus
Köninger et al. (2013)	Reproductive Biology and Endocrinology	Germany	1995–2012	Prospective and retrospective components	Cohort 1: Cross-sectional Cohorts 2–4: Longitudinal	554 patients	Cross-sectional (450 women): 1 per patient Longitudinal: 3 per patient for 15 women, 2 per patient for 69 women, 5 per patient for 20 women	Samples were analysed stratified by age groups	AMH fluctuations during pregnancy and post-partum
Santillan et al. (2012)	Reproductive Sciences	USA	Not reported	Retrospective	Cross-sectional	107 women	1 per patient	Not reported	Association of fetal sex with maternal AMH levels
Nelson et al. (2010)	Fertility and Sterility	UK	Not reported	Prospective	Longitudinal cohort	60 women	4 per patient	Not reported	Association of advancing gestation and maternal adiposity with AMH
Plante et al. (2010)	Journal of Assisted Reproduction and Genetics	USA	2004–2007	Retrospective	Case-control	213 women	1 per patient	Only singleton pregnancies included	Association of reduced ovarian reserve (measured using AMH) with fetal aneuploidy
Li et al. (2010)	Prenatal Diagnosis	China	Not reported	Retrospective	Case-control	435 patients	1 per patient	Cases were matched with controls for maternal age and gestational age	Association of maternal serum AMH levels with the presence of a trisomy 21 (Down Syndrome) pregnancy
La Marca et al. (2005)	Human Reproduction	Italy/Israel	Not reported	Prospective	Cross-sectional	84 women	1 per patient	Not reported	AMH modifications during pregnancy

Table 3 – Clinical and assay characteristics of the included studies.

Study	Population	Age of women (years)	Gestational age at measurement	AMH assay used	Sample storage	Sensitivity or lowest limit of detection (pmol/l)	Inter-assay and intra-assay coefficient of variation (%)
Stegmann et al. (2015)	Inclusion criteria: women of any age who delivered a singleton after 20 weeks' gestation, who had elected to undergo integrated prenatal screening in Iowa between 2009 and 2010 and who had paired first and second trimester serum samples stored in the serum tissue bank. Exclusion criteria: non-spontaneous pre-term birth, non-white race.	Cases: 28.8 ± 5.2[a] Controls: 28.8 ± 5.5[a]	10–13.9 weeks and 15–20.9 weeks	An in-house assay, Reprosource, based on research-use-only materials and reagents from Beckman Coulter-DSL	All samples were frozen at −80°C until time of measurement	0.7	5–9 / 7–12
Gerli et al. (2015)	Study group Inclusion criteria: singleton pregnancies with gestational diabetes diagnosed by 75 g oral glucose tolerance test between 24 and 28 weeks of gestation Exclusion criteria: diabetes mellitus type I and type II, and multiple pregnancies Control group: Inclusion criteria: women with singleton healthy pregnancies Exclusion criteria: any previous history of metabolic disorders during pregnancy or a previous diagnosis of diabetes mellitus	Study group: 36.7 ± 4.3[a] Control group: 32.7 ± 4.5[a]	28–32 weeks 34–46 weeks 40 days after delivery	Gen II AMH ELISA (Beckman-Coulter)	Not reported	0.6	4.63 / 4.02
Köninger et al. (2013)	Inclusion criteria: Natural conception without artificial infertility treatment Exclusion criteria: History of ovarian surgery, infertility, chemotherapy or radiation.	30.8 ± 6.2[a]	Cross-sectional component: First trimester ≤14th week of gestation (*n* = 58) Second trimester 15–28 weeks (*n* = 53) Third trimester ≥29th week of gestation (*n* = 339) Longitudinal components: 15 women had samples taken in each trimester 69 women were sampled during admission for delivery and within 4 days post-partum 20 women had blood samples taken just before delivery and during each of the first 4 days post-partum	Gen II AMH ELISA (Beckman-Coulter, Immunotech, Webster, Texas, USA)	Not reported	0.6	Not reported
Santillan et al. (2012)	Inclusion criteria: Women ≥18 with an uncomplicated singleton delivery at ≥37 weeks. All samples were obtained from the Maternal-Fetal Tissue Bank at the University of Iowa. Exclusion criteria: None reported	Not reported	≥10 weeks to ≤40 weeks	Gen II AMH ELISA (Beckman-Coulter)	Not reported	Not reported	Not reported
Nelson et al. (2010)	Inclusion criteria: Women with spontaneous conception Exclusion criteria: Women with previous polycystic ovary syndrome, pre-eclampsia, gestational diabetes, or other metabolic complication of pregnancy developed during index pregnancy	Not reported	First, second and third trimester and ≥12 weeks after delivery	DSL AMH ELISA (Webster, TX)	All samples per subject were assayed within the same assay	Not reported	Not reported

(*continued on next page*)

Table 3 – (*continued*)

Study	Population	Age of women (years)	Gestational age at measurement	AMH assay used	Sample storage	Sensitivity or lowest limit of detection (pmol/l)	Inter-assay and intra-assay coefficient of variation (%)
Plante et al. (2010)	Inclusion criteria: Women with singleton pregnancies who underwent both maternal serum screening for fetal aneuploidy (with sufficient stored serum available) and chorionic villus sampling or amniocentesis (with available cytogenetic results) between 11th and 24th weeks of gestation at the University of North Carolina between 2004 and 2007. Exclusion criteria: None reported	32.9 ± 6.9[a]	First or second trimester between 11 and 24 weeks	Beckman-Coulter AMH ELISA (AMHbc) and DSL AMH ELISA (Diagnostic Systems Laboratories) (AMHdsl)	Stored at –80°C	AMHbc: 0.7 AMHdsl: 0.1	AMHbc: 9 / 4 AMHdsl: 5 / 3
Li et al. (2010)	Inclusion criteria: Women 20–48 years old with Down syndrome pregnancies (cases) or non-Down syndrome pregnancies (controls) were selected from the database of biochemical Down Syndrome screening at the University of Hong Kong. Exclusion criteria: None reported	37[b]	Between 11 and 13 weeks or 15 and 20 weeks	Gen II AMH ELISA (Immunotech, Beckman-Coulter, France)	Samples were stored at –20°C	Not reported	14.2 / 12.3
La Marca et al. (2005)	Inclusion criteria: Group A: Nulliparae healthy women, not seeking pregnancy and with normal BMI; Groups B–E: Primigravidae women with singleton pregnancies at different gestational ages Exclusion criteria: Women with a known history of thyroid dysfunction, diabetes mellitus or any personal or familial immune disease.	A: 18–32 B: 19–35 C: 17–34 D: 20–37 E: 20–35	Group A: control non-pregnant women Group B: weeks 9–11 Group C: weeks 21–23 Group D: weeks 36–38 Group E: between 48 and 72 h post-delivery	AMH ELISA (Immunotech, Beckman-Coulter, France)	Storage of samples prior to measurement is not reported	0.7	8.7 / 5.3

[a] Mean ± SD.
[b] Median.

Table 4 – AMH values for each trimester in the included studies.

Study	First trimester		Second trimester		Third trimester		Post-partum	
	Gestational age (weeks)	AMH value (pmol/l)	Gestational age (weeks)	AMH value (pmol/l)	Gestational age (weeks)	AMH value (pmol/l)	Timing of measurement	AMH value (pmol/l)
Stegmann et al. (2015) Control group	10–13.9[a]	25.70 ± 18.56[b]	15–20.9[a]	21.42 ± 16.42[b]	–	–	–	–
Stegmann et al. (2015) Cases group	10–13.9[a]	22.13 ± 17.14[b]	15–20.9[a]	19.99 ± 14.99[b]	–	–	–	–
Gerli et al. (2015) Control group	–	–	–	–	28–32[a] 34–36[a]	5.71 (0.71–32.13)[c] 4.28 (0.71–17.85)[c]	40 days	7.14 (0.71–104.96)[c]
Gerli et al. (2015) Cases group	–	–	–	–	28–32[a] 34–36[a]	6.43 (0.71–24.99)[c] 5.00 (0.71–27.85)[c]	40 days	10.00 (0.71–49.98)[c]
Köninger et al. (2013) Cross-sectional component	≤14	12.07 (12.21–22.13)[c]	15–28[a]	5.71 (3.43–10.07)[c]	≥29th week of gestation[a]	3.57 (1.29–7.14)[c]	–	–
Köninger et al. (2013) Longitudinal components	≤14	19.49 (13.35–23.21)[c]	15–28[a]	16.85 (11.35–21.06)[c]	≥29th week of gestation[a]	9.85 (7.35–12.28)[c]	–	–
Köninger et al. (2013) Post-partum component	–	–	–	–	Before delivery (n = 69)	4.07 (1.29–8.21)[c]	During first 4 days post-partum (n = 69) Day 1 post-partum (n = 20) Day 4 post-partum (n = 20)	3.00 (1.00–6.43)[c] 1.43 (0.29–4.00)[c] 2.57 (1.07–4.14)[c]
Santillan et al. (2012)	Not reported	16.99 ± 14.28[b]	Not reported	12.93 ± 11.42[b]	Not reported	5.93 ± 6.64[b]	–	–
Nelson et al. (2010)	12.40 ± 1.50[b]	11.20 (7.60–20)[c]	26.10 ± 1.30[b]	8.60 (3.60–13.0)[c]	35.50 ± 1.30[b]	5.50 (2.20–9.20)[c]	17.30 ± 2.90 weeks after delivery[b]	14.80 (7.70–26.0)[c]
Plante et al. (2010) (Beckman-Coulter values)	11–14[a]	20.20 ± 14.90[b]	15–24[a]	9.70 ± 8.40[b]	–	–	–	–
Li et al. (2010) Control group	11–13[a]	14.65 ± 8.64[b]	15–20[a]	9.83 ± 7.28[b]	–	–	–	–
Li et al. (2010) Cases group	11–13[a]	14.15 ± 10.00[b]	15–20[a]	10.40 ± 7.66[b]	–	–	–	–
La Marca et al. (2005)	9–11[a]	14.99 ± 4.00[b]	21–33[a]	17.14 ± 4.57[b]	36–38[a]	13.92 ± 4.28[b]	48–72 h post-partum	15.35 ± 3.93[b]

[a] Range (min–max).
[b] Mean ± SD.
[c] Median (interquartile range).

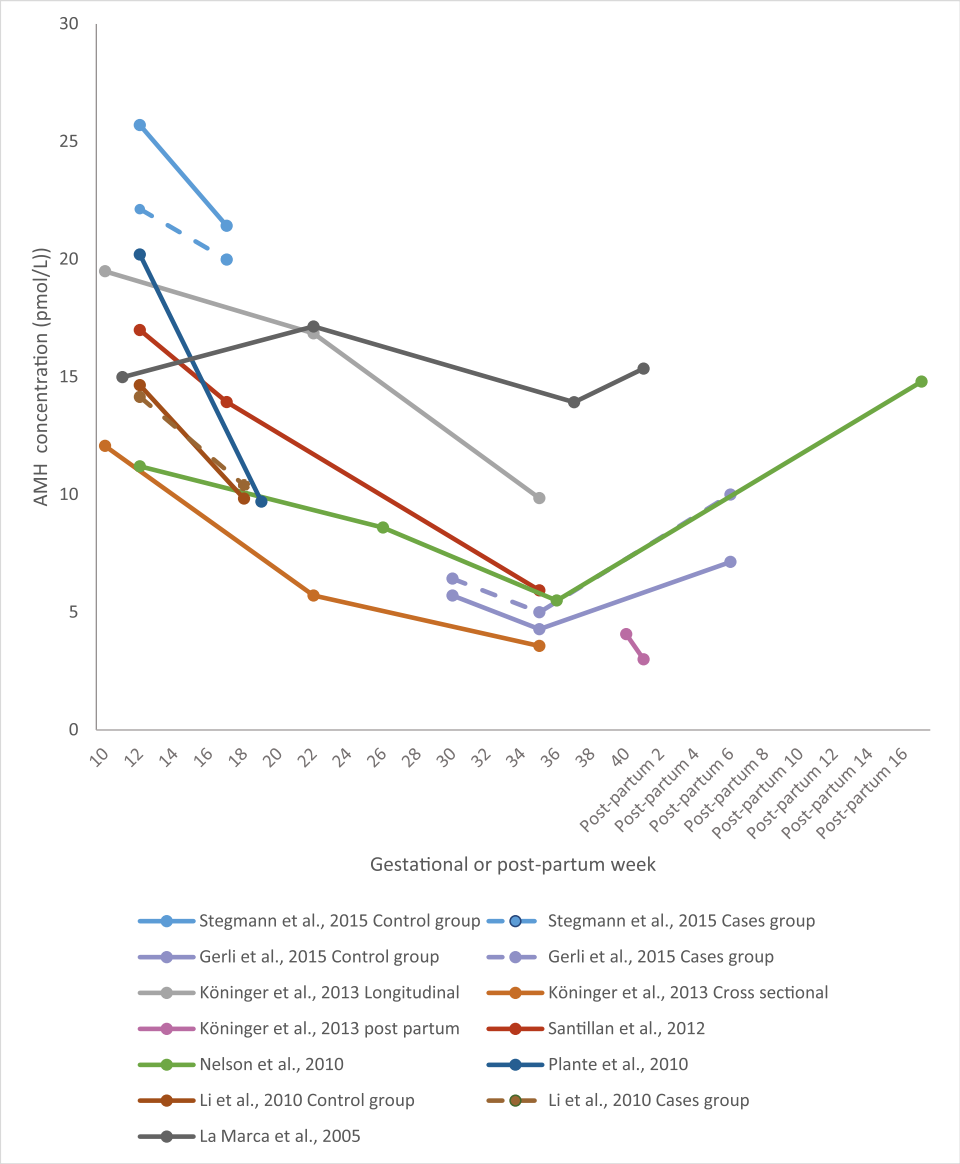

Figure 2 – Anti-Müllerian hormone concentrations during pregnancy or post-partum.

age, with AMHbc 20.2 ± 14.9 pmol/l in the first trimester and 9.7 ± 8.4 pmol/l in the second. It should be noted that in this study, first and second trimester AMH concentrations were provided for the whole study population, and no data were provided separately for cases (pregnancies with an aneuploidy embryo) or controls (pregnancies with a euploid embryo).

In singleton pregnancies not affected by Down syndrome, Li et al. (2010) found a first trimester AMH value of 14.65 ± 8.64 pmol/l and a second trimester value of 9.83 ± 7.28 pmol/l, which represents a statistically significant decrease. In the group of pregnancies with fetuses affected by Down syndrome a significant decrease in AMH concentrations was also observed (first trimester: 14.15 ± 10.00 pmol/l versus second trimester: 10.40 ± 7.66 pmol/l).

Santillan et al. (2012) found a significant fall in AMH between 11 and 15 weeks of pregnancy, with the mean serum AMH falling from 16.99 ± 14.28 pmol/l to 12.93 ± 11.42 pmol/l.

Second to third trimester changes

Four studies examined the kinetics of AMH between the second and third trimesters of pregnancy, with all four finding significant decreases in AMH concentrations over this period (Köninger et al., 2013; La Marca et al., 2005; Nelson et al., 2010; Santillan et al., 2012).

Nelson et al. (2010) found a significant decrease of 3.1 pmol/l in median AMH concentrations from the second trimester (8.6 pmol/l) to the third trimester (5.5 pmol/l). Santillan et al. (2012) also found a significant decrease from 12.93 ± 11.42 pmol/l to 5.93 ± 6.64 pmol/l over this period.

The longitudinal component of Köninger et al. (2013) found significant differences of 7 pmol/l between the second and third trimester values of 16.85 pmol/l and 9.85 pmol/l. The Köninger et al. (2013) cross-sectional component found a decrease of 2.14 pmol/l from the second

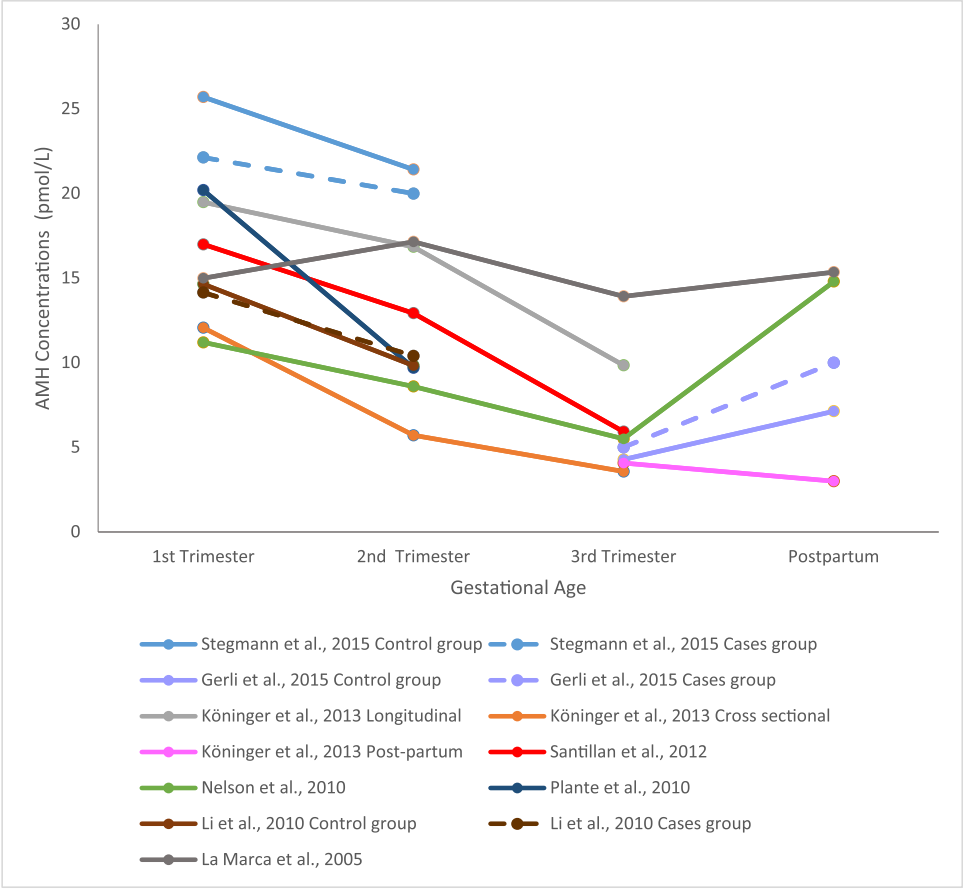

Figure 3 – Anti-Müllerian hormone and gestational age by trimester.

trimester (5.71 pmol/l) to the third trimester (3.57 pmol/l). When these results were stratified by age group the ≤27 years group had a significant difference between the median values for the first and third trimesters as well as the second and third trimesters, whilst the 28–34 years age group had significant differences between each trimester (first versus second, first versus third and second versus third). The ≥35 years age group had no significant differences in median AMH values between any trimesters.

La Marca et al. (2005) found a decrease in AMH concentrations between the second and third trimesters from 17.14 ± 4.57 pmol/l to 13.92 ± 4.28 pmol/l, respectively, although this difference was not statistically significant.

Gerli et al. (2015) examined AMH concentrations longitudinally by taking two measurements in the third trimester and another measurement 40 days after delivery. In the control group they found a significant decrease across the third trimester with a median AMH concentration of 5.17 pmol/l at 28–32 weeks and 4.28 pmol/l at 34–36 weeks. A similar, significant decrease in AMH was observed in the cases group (women with gestational diabetes mellitus), from 6.43 pmol/l at 28–32 weeks to 5.0 pmol/l at 34–36 weeks.

Third trimester to post-partum

Köninger et al. (2013) also analysed AMH concentrations pre- and post-partum, finding that AMH significantly decreases shortly after birth with a median concentration of 1.43 pmol/l on day 1 post-partum and then significantly increases to 2.57 pmol/l on day 4 post-partum. Similarly, La Marca et al. (2005) found a non-significant increase in AMH in the 48 to 72 h post-partum.

Nelson et al. (2010) took an AMH measurement at a mean of 17.3 ± 2.9 weeks postnatally, which found that AMH concentrations were significantly higher than the values during pregnancy. Gerli et al. (2015) also found a significant increase from the third trimester median AMH value to the post-partum values in both control and case groups, with changes from 4.28 pmol/l to 7.14 pmol/l and 5.00 pmol/l to 10.00 pmol/l, respectively.

Discussion

This systematic review suggests that during pregnancy the serum AMH concentration declines with advancing gestational age. This finding is supported by seven out of eight studies that have been analysed. The only study not completely in line with this conclusion is the La Marca et al. (2005) study in which an increase between the first and second trimesters was noted. However, this is a cross-sectional study and this might mean that this difference could be confounded by other variables, such as maternal age.

Furthermore, following delivery it appears that serum AMH concentration increases. This was supported by three of the studies that evaluated pre- and post-delivery AMH concentrations (Gerli et al., 2015;

La Marca et al., 2005; Nelson et al., 2010), but not by Köninger et al. (2013). The reason behind the result observed in the latter study is not clear. It should be noted, however, that the Beckman-Coulter Gen II assay used in that study has been shown to result in inconsistent AMH results under certain sample handling conditions (Han et al., 2014).

Reasons for the inverse relationship between gestational age and AMH concentrations are unclear, but there are several possible mechanisms. The reduced concentration of AMH during pregnancy is consistent with the decrease in serum AMH concentration observed during treatment with hormonal contraception (Dewailly et al., 2014). This may imply that suppressed gonadotrophin release (La Marca et al., 2013) and increased concentrations of circulating progesterone and/or oestrogen during pregnancy (Kuijper et al., 2013) could inhibit follicular recruitment.

Importantly, the decreased AMH concentrations may suggest reduced ovarian follicular activity in pregnancy with a potentially fertility preserving function. However, as AMH still remains detectable at these reduced concentrations we can assume that the ovaries do not completely enter quiescence, with some follicular recruitment remaining. Decreased ovarian follicular activity during pregnancy would be consistent with the findings by some epidemiological studies that increased parity is associated with a delay in menopausal onset (Cramer and Xu, 1996; Gold et al., 2001; Whelan et al., 1990).

The post-partum increase in AMH indicates that the presumed inhibition of follicular recruitment during pregnancy is released following birth. Interestingly, an increase is similarly observed in serum AMH following the cessation of hormonal contraceptives (La Marca et al., 2013; van den Berg et al., 2010).

Studies examining AMH concentrations during the post-partum period do not report whether the women were breastfeeding or on hormonal contraceptives, which may confound the results and explain the discrepancies in post-partum AMH values between studies. As association between breastfeeding and AMH concentrations is yet to be studied, a potential downregulating effect of breastfeeding through prolactin on AMH concentration cannot be excluded. Nevertheless, limited evidence suggests normal AMH concentrations in women with hyperprolactinaemia (Barbakadze and Kristasashvili, 2014; Li et al., 2011).

La Marca et al. (2013) postulate that the reduction in serum AMH concentration could be associated with haemodilution due to pregnancy-related increased blood volume. Plasma volume expands throughout pregnancy, especially during the second trimester (Pritchard, 1965), and this is not associated with a proportionate increase in erythrocyte mass, often leading to a dilutional anaemia (Milman et al., 2007). Similarly, there may be a disproportionate increase in plasma volume compared with AMH production, causing a relative decrease in serum AMH concentration, rather than a change in ovarian AMH production. La Marca et al. (2013) also postulated that the serum AMH decrease in pregnancy could be associated with increased plasma–protein binding, although the exact physiological mechanism by which this might occur is not described.

Another potential explanation for the decreased serum AMH with increased gestation may be increased maternal adiposity and body mass index (BMI), which have been previously suggested to be negatively associated with AMH serum concentration (Freeman et al., 2007; Moy et al., 2015; Nelson et al., 2010). Nevertheless, there is also evidence that refutes such an association (Kriseman et al., 2015; Skałba et al., 2011; Woo et al., 2012) and hence it is unclear whether BMI and maternal adiposity are responsible for the AMH serum decline. However, the relatively rapid increase of AMH post-delivery might suggest that this is not the most likely cause.

This review used a systematic approach, included all available evidence, critically evaluated the methodology of the included studies and presented the results homogeneously for comparison. It should be noted that the conclusions drawn by this review must be interpreted with caution considering the fact that a limited number of studies have employed a longitudinal design. Nevertheless, although longitudinal studies are considered optimal for evaluating AMH kinetics during pregnancy, the cross-sectional studies demonstrated the same trends, apart from the La Marca et al. (2005) study.

Furthermore, there is heterogeneity in terms of the population studied. It should be noted that the included studies have not necessarily assessed AMH kinetics on healthy, unselected pregnancies. More specifically, in certain studies specific types of population were analysed such as women with or without: (i) pre-term birth (Stegmann et al., 2015), (ii) gestational diabetes mellitus (Gerli et al., 2015) and (iii) Down syndrome fetuses (Li et al., 2010). Interestingly, a negative association between gestational age and AMH concentration was observed in all these groups.

The variability in the serum AMH concentrations reported in the studies analysed in this systematic review can also potentially be attributed to heterogeneity in the study populations. AMH is known to decrease with increasing age, so studies with differences in the mean maternal age of participants (**Table 3**) could be expected to have different distribution of AMH concentrations. Further, other maternal factors such as BMI, smoking status and ethnicity have been reported to affect serum AMH concentrations (Dewailly et al., 2014; La Marca et al., 2013) and hence differences in these factors between the analysed studies could partially explain the differences in the observed AMH values. Additionally, there were differences in the timing of the measurements and the assay used, which might explain some of the discrepancies observed.

Importantly, despite these differences, the general trend from the analysed studies is that there is a decline in serum AMH across gestation, which seems to recover post-partum. These differences also do not allow the statistical synthesis of the results from individual studies. More specifically, the various AMH assays used in the eligible studies have been shown to produce quantitatively different results without a straightforward and accurate method of converting them to a common scale (Nelson and La Marca, 2011). Hence, although the comparison of AMH values between different time points within the same study is valid, pooling these results across different studies would be problematic. A potential method through which the results from individual studies could be compared in a meaningful way would be the assessment of the mean proportion of AMH decline per patient. Unfortunately, these data were not available.

The results of this review indicate that a large, longitudinal study would be useful to confirm the variation of AMH with gestational age and further assess the potential physiological mechanisms which cause the decline. Repeated measurements in the same subjects, at fixed time points, would give more robust data, eliminating the issues associated with the large AMH inter-individual variability (La Marca et al., 2013; Overbeek et al., 2012). Regarding the implications for clinical practice, this systematic review suggests that AMH concentration during pregnancy should not be used as a marker for ovarian reserve, especially using nomograms developed with non-pregnant patient data.

However, the measurement of AMH during pregnancy could potentially be useful because there is some data suggesting that it could

be used to predict pre-term birth, when modelled in conjunction with maternal serum α-fetoprotein and maternal weight change between first and second trimesters (Stegmann et al., 2015). AMH has also been reported to be associated with fetal sex by Santillan et al. (2012), who found that serum AMH concentrations are significantly higher in pregnancies carrying male fetuses compared with female fetuses.

In conclusion, this review has demonstrated an association between reduced maternal serum AMH concentrations and advancing gestational age. These findings suggest that AMH measurements in pregnant women, especially at later stages of pregnancy, should not be used to assess ovarian reserve. Furthermore, future research on a longitudinal cohort is needed in order to more accurately assess AMH concentrations during pregnancy and elucidate whether ovarian activity is indeed reduced. If this hypothesis is confirmed, further research might explore the physiological mechanisms which cause this decreased ovarian activity during pregnancy.

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