Reproductive BioMedicine Online (2013) 27, 33–63

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REVIEW

Reproductive hormone concentrations in pregnancy and neonates: a systematic review

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Esther AM Kuijper was born 6 February 1977 in Alkmaar, The Netherlands. She studied medicine at the VU University Medical Center in Amsterdam She is a PhD student working on a thesis entitled 'Comparison of perinatal reproductive hormone status between familial dizygotic twins, non-familial dizygotic twins, monozygotic twins, singletons and their mothers'. Her current research interests are twins and endocrinology.

Abstract Although much research focuses on hormones during gestation, little is known about the actual hormone concentrations within the fetal surroundings. The aim of this study was to combine all available oestrogen, androgen, sex hormone-binding globulin (SHBG), anti-Müllerian hormone (AMH), inhibin, gonadotrophin and dehydroepiandrosterone sulphate (DHEAS) concentrations during gestation and post partum into graphical representations reporting weighted mean hormone values. A systematic search was performed in Pubmed and Embase from inception to March 2012. Studies were evaluated by two reviewers; manuscripts were included if the actual hormone concentrations were reported together with the gestational age at time of sampling. A total of 97 articles were found eligible for this review. Maternal serum oestrogens, inhibin A, SHBG, androstenedione and testosterone rise during gestation, which is followed by a rapid decline in the post-partum period. For AMH and DHEAS, an inverse relationship is found, while gonadotrophin concentrations are negligible during gestation. For girls cord blood oestriol and post-partum FSH concentrations are higher, while for boys cord blood FSH and neonatal testosterone, inhibin B, LH and AMH concentrations are higher. In conclusion, longitudinally measured endocrine data during gestation and in the peri- and post-natal period are lacking, especially for twin pregnancies.

KEYWORDS: hormones, pregnancy, singletons, twins, post-partum, serum

Introduction

Since the introduction of the Barker hypothesis (fetal origin of disease in later life), much research has focused on the intrauterine environment and how it influences the developing fetus (Barker, 2007). For example, gender-related play behaviour (van de Beek et al., 2009), development of autistic disorders (Iwata et al., 2011), polycystic ovary syndrome (PCOS; Cattrall et al., 2005), metabolic syndrome and cardiovascular disease (Rogers and Velten, 2011) have all been suggested to be associated with hormonal changes during gestation. Furthermore, elevated maternal testosterone

1472-6483/$ - see front matter
http://dx.doi.org/10.1016/j.rbmo.2013.03.009

concentrations might be associated with intrauterine growth restriction (Carlsen et al., 2006), peri-partum depression (Hohlagschwandtner et al., 2001) and pre-eclampsia (Carlsen et al., 2005; Serin et al., 2001). The fetus is influenced by endogenous hormones as well as by maternal hormones, through placental passage, biological activity and receptor affinity. As fetal blood sampling involves risks for the ongoing pregnancy, substitutes have been used to evaluate hormonal exposure during gestation, for example by using maternal serum or amniotic fluid. However, poor correlations between maternal serum samples and umbilical cord blood have been reported (Troisi et al., 2003c). Therefore, little is known about the actual hormone concentrations affecting the developing fetus. Maternal hormones larger than 0.7 kDa are almost unable to pass the placenta to the fetal compartment and therefore, the fetal endocrine milieu is largely independent of maternal hormones. However, steroids are highly lipophilic and cross the placenta in both directions, but most of them are metabolized en route (Fisher, 1986; Petraglia et al., 1991).

For multiple pregnancies, this situation is even more complex because circulating hormones both influence and are influenced by at least two fetuses. For example, it was suggested that higher oestrogen exposure in dizygotic twins could play a role in the development of hormone-related tumours such as breast, prostate or testicular cancer (Swerdlow et al., 1997; Trichopoulos, 1990). Possible indicators of fetal oestrogen exposure such as birth size parameters (length, weight) and maternal diet have been evaluated in this context (Lagiou et al., 2006; Mucci et al., 2003; Nagata et al., 2006; Troisi et al., 2003b). To date, an overview of studies reporting actual endocrine data during gestation and in early childhood is lacking. Therefore, the aim of the current study was to systematically review all available literature on reproductive hormone concentrations in singleton and twin pregnancies and neonates up until 6 months after birth.

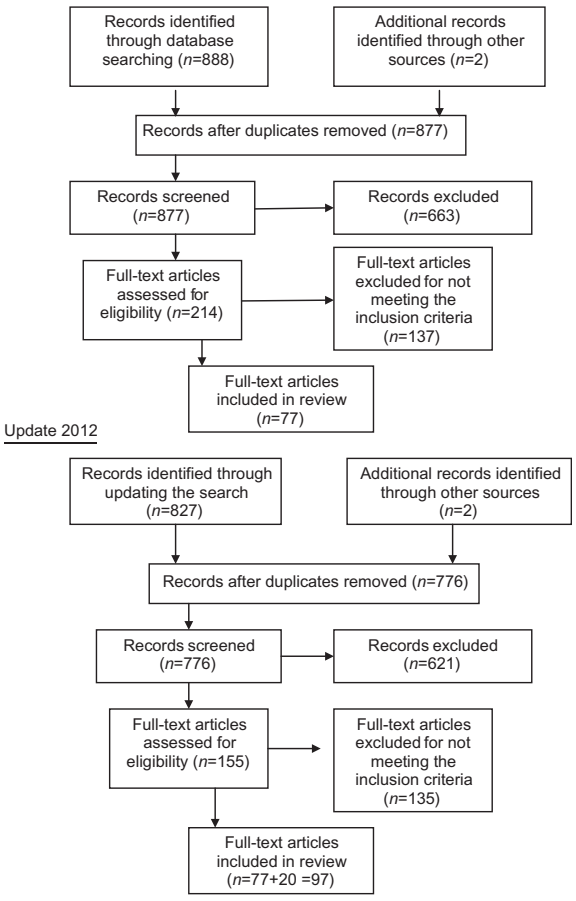

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Metal-Analyses) flow diagram indicating the number of articles searched and included in this review.

Materials and methods

The PubMed and Embase databases were searched for relevant studies from inception to 7 May 2010. For this litera-

Table 1 An exemplary strategy for the PubMed search (7 May 2010).

Search number	*Query*	*Result*
1	'Pregnancy'[majr] OR ('pregnancy trimester, second'[MeSH] OR 'pregnancy trimester, third'[MeSH]	143,089
2	'Fetal blood'[MeSH]	21,992
3	'Infant, newborn'[MeSH] OR 'amniotic fluid'[MeSH]	444,369
4	Neonate*[tiab] OR infant*[tiab] OR newborn*[tiab] OR amniotic[tiab] OR 'umbilical cord'[tiab] OR 'maternal serum'[tiab]	383,973
5	1 OR 2 OR 3 OR 4	752,739
6	Follitropin[tiab] OR 'luteinizing hormone'[tiab] OR oestrogen*[tiab] OR testosterone[tiab] OR androstenedione[tiab] OR 'sex hormone-binding globulin'[tiab] OR 'Müllerian inhibiting factor'[tiab] OR inhibin*[tiab] OR androgen*[tiab]	187,180
7	'Follicle-stimulating hormone'[MeSH:noexp] OR 'luteinizing hormone'[MeSH] OR 'estrogens'[MeSH:noexp] OR 'testosterone'[MeSH:noexp] OR 'androstenedione'[MeSH] OR 'sex hormone-binding globulin'[MeSH] OR 'anti-Müllerian hormone'[MeSH] OR 'inhibins'[MeSH:noexp]	137,821
8	6 OR 7	241,940
9	'Epidemiologic studies'[MeSH] NOT 'reproductive techniques, assisted'[MeSH]	1,192,466
10	5 and 8 and 9	584

Majr = major; tiab = title/abstract.

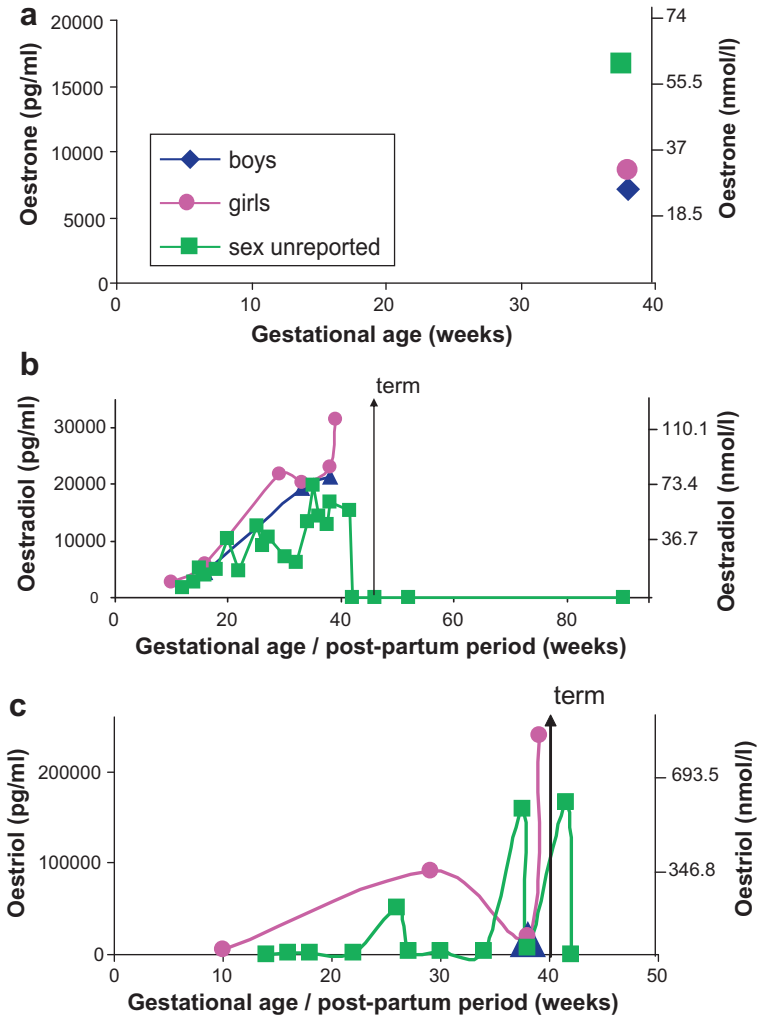

Figure 2 Weighted means of all reported maternal serum oestrogen concentrations (**a**, oestrone; **b**, oestradiol; **c**, oestriol) during gestation, at term and in the post-partum period. Data from Serin et al. (2001) are not included in (**b**).

Table 2 Maternal serum oestrone concentrations during gestation.

Gestational age (weeks)	*Girls*		*Boys*		*Sex unreported*		*Study*
	Oestrone (pg/ml)	n	*Oestrone (pg/ml)*	n	*Oestrone (pg/ml)*	n	
37–38					5090	86	Troisi et al. (2003d)
37–38					28,135	86	Troisi et al. (2003a)
38	7640	86	6098	86			Troisi et al. (2003b)
38	9595	86	8151	86			Troisi et al. (2003c)

ture search, the following terms were used (with synonyms and closely related words) as thesaurus terms and free text words: 'pregnancy', 'fetal blood' or 'neonate' and 'follicle-stimulating hormone (FSH)', 'luteinizing hormone (LH)', 'estrogens', 'androstenedione', 'sex hormone-binding globulin (SHBG)', 'anti-Müllerian hormone (AMH)', 'inhibins' or 'testosterone' and 'epidemiologic studies'. The full search strategies for both databases can be requested from the corresponding author. An exemplary search strategy from PubMed is presented in **Table 1**.

In addition, the reference lists of the included studies and relevant reviews were screened for missed articles. The abstracts of all citations identified by the literature search were independently screened by two reviewers. Both reviewers are medical doctors, one is a PhD student and one is a reproductive endocrinology professor. Possible relevant articles were included or rejected based on the full text paper. Any discrepancies were solved by consensus.

Oestrogens (oestrone, oestradiol and oestriol), androgens (testosterone, androstenedione, dehydroepiandrosterone

Table 3 Maternal serum oestradiol concentrations during gestation and post partum.

	Girls		*Boys*		*Sex unreported*		*Study*
	Oestradiol (pg/ml)	n	*Oestradiol (pg/ml)*	n	*Oestradiol (pg/ml)*	n	
Gestational age (weeks)							
10	2687	194					Nagata et al. (2006)
12					2300	60	Nelson et al. (2010)
12					874.6	51	Soldin et al. (2005)
12–20			2582.3	112			Thomas et al. (1998)
14					2778.4	10	Kerlan et al. (1994)
15					5175.4	12	Sattar et al. (1999)
15–18	6153	79	6077	77			van de Beek et al. (2004)
15–18	5979	59	5976	61			van de Beek et al. (2009)
16					3840.7	53	Lagiou et al. (2003)
16					3868	230	Mucci et al. (2003)
18					4930.3	10	Kerlan et al. (1994)
20					10,541.5	12	Sattar et al. (1999)
22					7163.9	10	Kerlan et al. (1994)
22					4234.6	50	Soldin et al. (2005)
25					12,584.4	12	Sattar et al. (1999)
26					10,514.3	10	Kerlan et al. (1994)
26					9640	60	Nelson et al. (2010)
26					8961.6	456	Smith et al. (2009)
27					10,459.8	53	Lagiou et al. (2003)
27					10,759.4	230	Mucci et al. (2003)
28–32					92.2	20	Serin et al. (2001)
29	21,734	194					Nagata et al. (2006)
30					11,140.8	10	Kerlan et al. (1994)
30					15,825.9	12	Sattar et al. (1999)
30–35	20,348	79	19,435	77			van de Beek et al. (2004)
32					6177.8	50	Soldin et al. (2005)
34					13,483.3	10	Kerlan et al. (1994)
35					19,884.5	12	Sattar et al. (1999)
36					12,745	60	Nelson et al. (2010)
36					25,475.4	9	Dzaja et al. (2009)
37–38					18,370	86	Troisi et al. (2003d)
37–38					7526	86	Troisi et al. (2003a)
37–39	19,254	31	16,741	29			Gol et al. (2004)
38					16,888.2	10	Kerlan et al. (1994)
38	23,049	86	20,445	86			Troisi et al. (2003b)
38	24,691	86	23,735	86			Troisi et al. (2003c)
38–40	31,419	194					Nagata et al. (2006)
41–42					15,331.5	489	Carlsen and Heimstad (2011)
Post partum (days)							
4					27.2	10	Kerlan et al. (1994)
42					35	60	Nelson et al. (2010)
84					40.7	20	Serin et al. (2001)
90					94.9	9	Dzaja et al. (2009)

sulphate), SHBG, LH, FSH, inhibins (A and B) and AMH were included in the search. Cohort studies, reviews and case–control studies (using the control group) were included and animal studies and case-reports were excluded. Study validity was checked using a Cochrane checklist (available at dcc.cochrane.org). A study was found eligible if the language of publication was English and the actual hormone concentrations were reported together with the gestational age at time of sampling. Neonatal data were included up until 6 months of age. Hormone measurements

Table 4 Maternal serum oestriol concentrations during gestation and post partum.

	Girls		*Boys*		*Sex unreported*		*Study*
	Oestriol (pg/ml)	n	*Oestriol (pg/ml)*	n	*Oestriol (pg/ml)*	n	
Gestational age (weeks)							
10	5700	194					Nagata et al. (2006)
14					288.4	10	Kerlan et al. (1994)
16					1095.8	53	Lagiou et al. (2003)
16					1124.7	270	Lagiou et al. (2006)
16					1095.8	230	Mucci et al. (2003)
18					1182.4	10	Kerlan et al. (1994)
22					1874.5	10	Kerlan et al. (1994)
26					2451.2	10	Kerlan et al. (1994)
26					52,680.1	456	Smith et al. (2009)
27					4037.3	53	Lagiou et al. (2003)
27					4037.3	270	Lagiou et al. (2006)
27					4037.3	230	Mucci et al. (2003)
29	91,000	194					Nagata et al. (2006)
30					3691.3	10	Kerlan et al. (1994)
34					4268	10	Kerlan et al. (1994)
37—38					15,000	86	Troisi et al. (2003d)
37—38					303,000	86	Troisi et al. (2003a)
38					8017	10	Kerlan et al. (1994)
38	18,500	86	15,100	86			Troisi et al. (2003b)
38	20,000	86	17,000	86			Troisi et al. (2003c)
38—40	239,400	194					Nagata et al. (2006)
41—42					167,260	489	Carlsen and Heimstad (2011)
Post partum (days)							
4					Undetectable	10	Kerlan et al. (1994)

could have been carried out in serum, amniotic fluid, saliva or urine.

The results of this search are given in **Figure 1**, which shows the PRISMA (Preferred Reporting Items for Systematic-reviews and Meta-analyses) flow diagram (Liberati et al., 2009). This search was updated and dehydroepiandrosterone sulphate (DHEAS) was added on 28 March 2012 resulting in an additional 20 articles. All figures and tables in this review give hormone concentrations converted (if necessary) to the same unit. To convert oestrogens from nmol/l to pg/ml, the formulae oestrone $\times$ 270.366, oestradiol $\times$ 272.39 and oestriol $\times$ 288.38 were used, and to convert androgens from nmol/l to ng/ml the formulae testosterone $\times$ 0.28843, DHEAS $\times$ 0.36849 and androstenedione $\times$ 0.2864 were used.

LH and FSH are always given in IU/l and therefore need no conversion, this also applied to inhibins (in ng/l or pg/ml) and SHBG (in nmol/l in all publications). To convert AMH from pmol/l to ng/ml, the formula AMH $\times$ 0.14 was used. Values represent weighted average hormonal values during gestation or in the first 6 months in neonates. Means were constructed by weighting the mean hormone value of an individual study with their group size and they were constructed when multiple studies were available at that specific time point (Hazewinkel, 2002). For example, for oestradiol in maternal serum at 12 weeks of gestation the weighted mean is ((2300 $\times$ 60) + (874.6 $\times$ 51))/(60 + 51) = 1637.2 pg/ml.

Results

Unless otherwise stated, the results are discussed from the perspective of singleton pregnancies and births. Twin pregnancies are discussed in a separate section.

Oestrogens

Oestrogens are primarily produced by developing follicles and by the corpus luteum; however, the placenta, liver, adrenal glands, fat and breast cells produce oestrogens as well (Grow, 2002). Oestradiol in women is produced mainly during the fertile lifespan, while oestrone is the predominant oestrogen during menopause and oestriol during pregnancy. Cholesterol-derived androgens are the common precursors of oestrogens. Androstenedione is converted to either oestrone or testosterone, which by aromatase activity is converted to oestradiol (Sanderson, 2009). After synthesis, oestradiol is immediately released into the bloodstream, where the majority is bound to albumin or

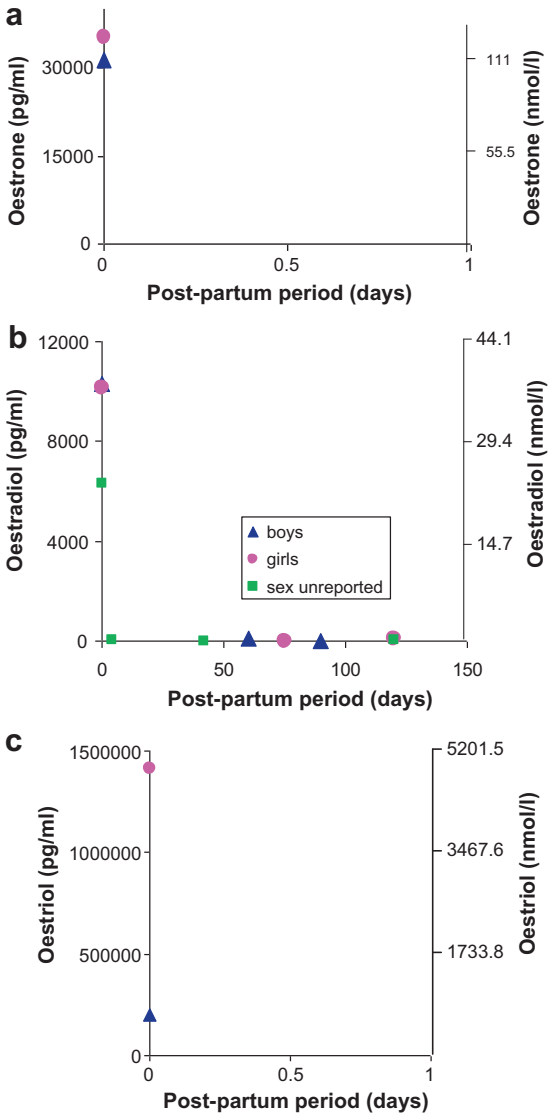

Figure 3 Weighted means of all reported fetal and neonatal serum oestrogen concentrations (**a**, oestrone; **b**, oestradiol; **c**, oestriol) at term and in the post-partum period.

SHBG. Only the unbound portion is biologically active. Oestradiol is cleared from the circulation either by conversion to other oestrogen forms (oestrone or oestriol) or by conjugation to products that are water soluble and excreted in the urine and bile (Speroff and Fritz, 2005).

During gestation, excretion of maternal oestrogen (oestradiol and oestrone) is increased about a 100-fold, while oestriol secretion is raised even more. This increase in maternal oestrogen concentrations and oestrogen production is dependent on fetal and placental co-operation. For example, fetal DHEAS is converted by 16α-hydroxylase, in the fetal liver, to form the precursor for oestriol. Shortly after birth this hepatic 16α-hydroxylation ability disappears (Speroff and Fritz, 2005).

Maternal samples

Limited data are available on maternal serum oestrone (oestrone) concentrations during gestation (**Figure 2A** and **Table 2**). One study from the 1990s reported a rise in oestrone concentrations (both in serum and urine) during pregnancy (Berg and Kuss, 1992). Most of the available data are by Troisi et al. (2003a,b,c,d), who found no differences for fetal gender at term (Troisi et al., 2003b,c). Salivary oestrone concentrations (36.75 pg/ml), at 37 weeks of gestation are much lower compared with serum concentrations (Marrs et al., 2007).

Oestradiol concentrations in maternal serum rise steadily from the first trimester until term and decline rapidly in the post-partum period, as demonstrated in **Figure 2B** and **Table 3** (Carlsen and Heimstad, 2011; Dzaja et al., 2009; Gol et al., 2004; Kerlan et al., 1994; Lagiou et al., 2003; Mucci et al., 2003; Nagata et al., 2006; Nelson et al., 2010; Sattar et al., 1999; Serin et al., 2001; Smith et al., 2009; Soldin et al., 2005; Thomas et al., 1998; Troisi et al., 2003a,b,c,d; van de Beek et al., 2004, 2009). Compared with all other studies, Serin et al. (2001) reported much lower oestradiol concentrations, which might be due to different hormone measuring techniques used; however, their post-partum values are well within the range reported by others. No sex-related differences were found in second- or third-trimester maternal serum oestradiol concentrations between women pregnant with a boy or a girl (Gol et al., 2004; Troisi et al., 2003b,c; van de Beek et al., 2004, 2009). Although, overall amniotic fluid oestradiol concentrations (gestational age 15–18 weeks) were lower compared with serum concentrations, female fetuses have significantly higher oestrogen concentrations compared with males (275.1 versus 239.1 pg/ml and 275.1 versus 242.4 pg/ml) (van de Beek et al., 2004, 2009). Salivary data showed oestradiol values of 15.9 pg/ml at 37 weeks of gestation (Marrs et al., 2007), again much lower compared with serum values. Furthermore, oestradiol concentrations during pregnancy are significantly higher in white women compared with black women (McGlynn et al., 2005).

Maternal serum oestriol concentrations, as expected, rise during gestation and are undetectable after birth (**Figure 2C** and **Table 4**; Berg and Kuss, 1992; Kerlan et al., 1994; Lagiou et al., 2006; Nagata et al., 2006; Peter

Table 5 Cord blood oestrone concentrations at term and post partum.

Post partum (days)	*Girls*		*Boys*		*Study*
	Oestrone (pg/ml)	n	*Oestrone (pg/ml)*	n	
0	25,750	53	24,740	61	Maccoby et al. (1979)
0	31,809	37	29,684	49	Troisi et al. (2003b)
0	42,742	86	37,305	86	Troisi et al. (2003c)

Table 6 Fetal/neonatal serum oestradiol concentrations at term and post partum.

Post partum (days)	*Girls*		*Boys*		*Sex unreported*		*Study*
	Oestradiol (pg/ml)	n	*Oestradiol (pg/ml)*	n	*Oestradiol (pg/ml)*	n	
0	18,606	14	10,067	7			Anderson et al. (2010)
0	8126	31	7321	29			Gol et al. (2004)
0	7530	53	8890	61			Maccoby et al. (1979)
0	8201	37	9617	49			Troisi et al. (2003b)
0	11,941	86	12,782	86			Troisi et al. (2003c)
0					6344	125	Simmons (1995)
4					27.2	10	Kerlan et al. (1994)
42					40.7	20	Serin et al. (2001)
60			95.3	23			Barthold et al. (2004)
60—90	10.2	21					Sir-Petermann et al. (2006)
90			4.9	270			Boas et al. (2006)
90			5.2	598			Mau et al. (2007)
120					35	60	Nelson et al. (2010)
120	91	10					Ibanez et al. (2002)

Table 7 Cord blood oestriol concentrations at term.

Post partum (days)	*Girls*		*Boys*		*Study*
	Oestriol (pg/ml)	n	*Oestriol (pg/ml)*	n	
0	2,126,000	194			Nagata et al. (2006)
0	254,000	37	180,000	49	Troisi et al. (2003b)
0	300,000	86	210,000	86	Troisi et al. (2003c)

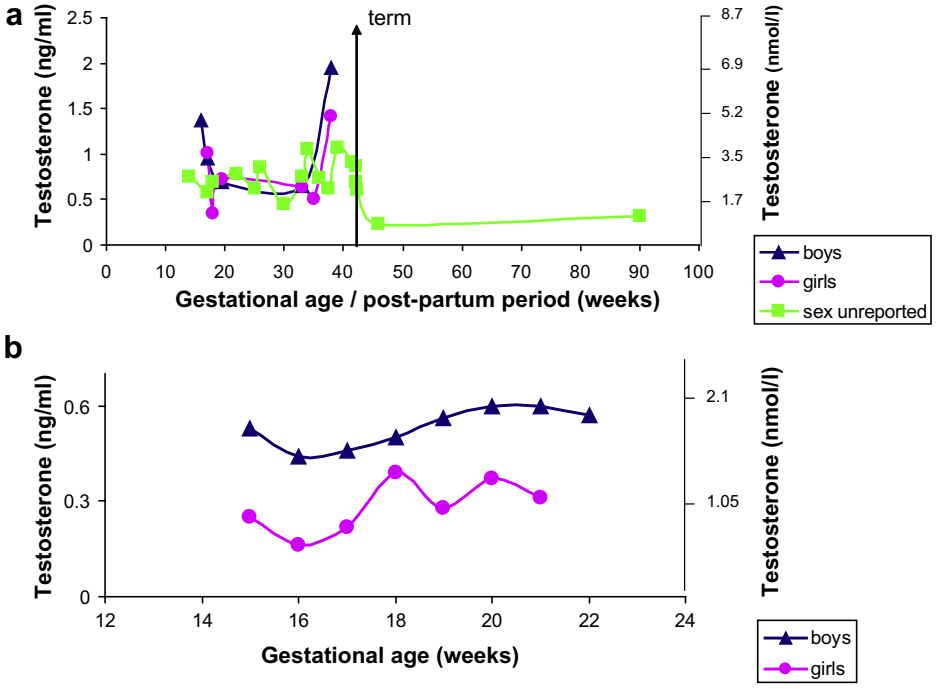

Figure 4 Weighted means of all reported maternal serum (**a**) and amniotic fluid (**b**) testosterone concentrations during gestation, at term and in the post-partum period. Data from Gol et al. (2004) are not included in (**a**).

Table 8 Maternal serum and amniotic fluid testosterone concentrations during gestation and post partum.

	Girls		*Boys*		*Sex unreported*		*Study*
	Testosterone (ng/ml)	n	*Testosterone (ng/ml)*	n	*Testosterone (ng/ml)*	n	
Maternal serum (weeks of gestation)							
12–20			1.37	38			Thomas et al. (1998)
14					0.75	10	Kerlan et al. (1994)
15–18	0.67	78	0.61	75			van de Beek et al. (2004)
15–18	2.06	56	1.96	56			van de Beek et al. (2009)
17					0.58	147	Carlsen et al. (2006)
17	0.52	64	0.52	71			Carlsen et al. (2005)
18	0.35	118					Hickey et al. (2010)
18					0.70	10	Kerlan et al. (1994)
19–20	0.72	91	0.69	91			Tuutti et al. (2011)
22					0.78	10	Kerlan et al. (1994)
25					0.62	63	Carlsen et al. (2010)
26					0.85	10	Kerlan et al. (1994)
28–32					0.243	20	Serin et al. (2001)
30					0.85	10	Kerlan et al. (1994)
30–35	0.67	78	0.66	75			van de Beek et al. (2004)
33					0.75	144	Carlsen et al. (2006)
33	0.61	64	0.64	70			Carlsen et al. (2005)
34					1.05	10	Kerlan et al. (1994)
34–36	0.50	114					Hickey et al. (2010)
36					0.74	9	Dzaja et al. (2009)
37–38					1.07	86	Troisi et al. (2003d)
37–38					0.16	86	Troisi et al. (2003a)
37–39	142.5	31	181.6	29			Gol et al. (2004)
38	1.47	86	2.12	86			Troisi et al. (2003c)
38					1	10	Kerlan et al. (1994)
38	1.31	37	1.62	46			Troisi et al. (2003b)
38–40					1.07	193	Hohlagschwandtner et al. (2001)
41–42					0.906	489	Carlsen and Heimstad (2011)
Amniotic fluid (weeks of gestation)							
11–21	0.095	100	0.239	112			Auyeung et al. (2009)
15	0.25	50	0.53	237			Anand-Ivell et al. (2008)
15–18	0.20	78	0.41	75			van de Beek et al. (2004)
15–18	0.20	61	0.41	61			van de Beek et al. (2009)
16	0.30	50	0.54	237			Anand-Ivell et al. (2008)
17	0.28	50	0.49	237			Anand-Ivell et al. (2008)
18	0.39	50	0.50	237			Anand-Ivell et al. (2008)
19	0.28	50	0.56	237			Anand-Ivell et al. (2008)
20	0.37	50	0.60	237			Anand-Ivell et al. (2008)
21	0.31	50	0.60	237			Anand-Ivell et al. (2008)
22			0.57	237			Anand-Ivell et al. (2008)
Maternal serum post partum (days)							
1					0.86	193	Hohlagschwandtner et al. (2001)
3					0.70	193	Hohlagschwandtner et al. (2001)
4					0.6	10	Kerlan et al. (1994)
42					0.234	20	Serin et al. (2001)
90					0.32	9	Dzaja et al. (2009)

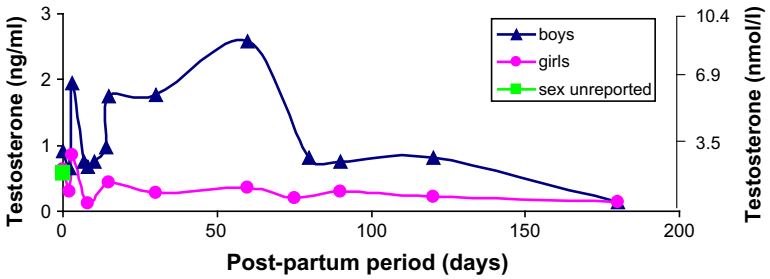

Figure 5 Weighted means of all reported fetal and neonatal serum testosterone concentrations at term and in the post-partum period. Data from Gol et al. (2004) and Whitehouse et al. (2010) are not included.

et al., 1994). Although, different authors report very different magnitudes of oestriol values at comparable gestational ages (Nagata et al., 2006; Smith et al., 2009; Troisi et al., 2003b,c), when comparing data within these studies, all authors report rising oestriol concentrations during pregnancy. Troisi et al. (2003b) reported a significant difference in maternal serum oestriol concentrations between women pregnant with a boy or a girl in one manuscript, but could not reproduce these results in another paper (Troisi et al., 2003c). Oestriol concentrations by Smith et al. (2009) are much higher compared with Nagata et al. (2006) and Schmidt et al. (2002)); however, their oestradiol concentrations are in line with other papers. This advocates against a difference in techniques used as an explanation for this difference. In contrast to oestradiol, oestriol amniotic fluid values (sex unreported) are higher compared with serum values at 16–17 weeks (4790 pg/ml) of gestation (Torricelli et al., 2009). Salivary oestriol concentrations (468.32 pg/ml) at term showed lower values compared with serum samples (Marrs et al., 2007). Urinary oestriol concentrations (mg/24 h) were respectively; 6.4 for 20–24 weeks, 12.4 for 25–29 weeks, 14.4 for 30–34 weeks and 18.8 for 35–39 weeks (Gonzalez et al., 1989). Oestriol concentrations during pregnancy are higher in white women compared with black women (McGlynn et al., 2005).

Overall, maternal serum and urinary oestrogens rise steadily until delivery and diminish after birth. Fetal sex does not seem to influence the oestrogen concentrations in maternal serum; however, in amniotic fluid it does. Compared with serum concentrations; amniotic fluid oestradiol concentrations are lower but oestriol concentrations are higher. Furthermore, ethnicity accounts for hormone differences as well.

Fetal/neonatal samples

Cord blood oestrone concentrations (**Figure 3A** and **Table 5**) are a little higher in girls compared with boys but do not differ significantly (Maccoby et al., 1979; Troisi et al., 2003b,c). There are no data available on oestrone concentrations in the post-partum period.

Serum oestradiol is high in cord blood but declines rapidly after birth (**Figure 3B** and **Table 6**). Conflicting outcomes are reported for fetal gender; some report higher oestradiol concentrations in girls (Anderson et al., 2010; Gol et al., 2004) and others in boys (Maccoby et al., 1979; Troisi et al., 2003b,c), but none of these were significant. Direct comparisons between boys and girls were done in all these studies except for the one by Anderson et al., which compared male and female offspring of PCOS mothers with offspring of non-PCOS mothers (Anderson et al., 2010). In neonates, low oestradiol concentrations have been reported in separate studies in boys and in girls but no comparison between neonatal gender has been made (Barthold et al., 2004; Boas et al., 2006; Ibanez et al., 2002; Mau et al., 2007).

As expected, oestriol is the most pronounced oestrogen in cord blood (**Figure 3C** and **Table 7**) and is reported to be significantly higher in females compared with males (Nagata et al., 2006; Troisi et al., 2003b,c). There are no data available on oestriol concentrations in the neonatal period.

Overall, in cord blood samples oestrogen concentrations are high. Highest values were found for oestriol, which is also the only oestrogen that shows gender-related differences (higher in girls compared with boys). In the neonatal period, oestradiol is the only present oestrogen but concentrations are low.

Androgens

Testosterone

Testosterone is primarily produced by the testes in males and the ovaries in females, although small amounts are also secreted by the adrenal glands in both sexes. Testosterone can be converted into either 5α-dihydrotestosterone by the enzyme 5α-reductase or into oestradiol by aromatase. 5α-dihydrotestosterone binds the androgen receptor with more affinity and therefore exerts more potent androgenic effects. While circulating in the bloodstream, the majority of testosterone is bound to SHBG (Speroff and Fritz, 2005). Throughout life, in males, testosterone has been known to exert different effects: for example during genital development during early gestation, the 'mini puberty' at about 4–6 months of age which might be involved in masculinization of the brain and the development of the secondary sexual characteristics at about puberty (Andersson et al., 1998; Kuiri-Hanninen et al., 2011). Adult women rely on testosterone mostly to maintain libido, bone density and muscle mass (Speroff and Fritz, 2005).

Effects of testosterone during gestation are most intensively studied in twins. Normally, placental aromatization is so efficient that almost all androgens presented to the placenta are converted. However, females that are born as part of an opposite-sex twin might be influenced by

Table 9 Fetal/neonatal serum testosterone concentrations.

	Girls		*Boys*		*Sex unreported*		*Study*
	Testosterone (ng/ml)	n	*Testosterone (ng/ml)*	n	*Testosterone (ng/ml)*	n	
Post partum (days)							
0	0.19	14	0.14	7			Anderson et al. (2010)
0	1.07	78	1.16	75			Van de Beek et al. (2004)
0	233.2	31	252.2	29			Gol et al. (2004)
0	1.95	58	2.39	80			Garagorri et al. (2008)
0	0.36	82					Hickey et al. (2010)
0	3712.7	78					Whitehouse et al. (2010)
0	0.22	86	0.29	86			Troisi et al. (2003c)
0	0.16	37	0.24	49			Troisi et al. (2003b)
0					0.58	125	Simmons (1995)
0	0.212	60	0.297	51			Maccoby et al. (1979)
0	0.30	20	0.39	22			Forest et al. (1974)
1—15	0.12	15	0.68	14			Forest et al. (1974)
1—30			0.1—2.91	215			Lahlou et al. (2004)
2	0.3	13	0.66	57			Bergada et al. (2006)
3	0.85	58	1.95	80			Garagorri et al. (2008)
7			0.76	57			Bergada et al. (2006)
10			0.76	57			Bergada et al. (2006)
14			0.98	57			Bergada et al. (2006)
15	0.43	58	1.75	80			Garagorri et al. (2008)
20			0.82	57			Bergada et al. (2006)
30	0.34	13	2.1	57			Bergada et al. (2006)
30			1.3	52			Cavarzere et al. (2010)
30	0.33	58	1.81	80			Garagorri et al. (2008)
30—90			0.52—4.79	215			Lahlou et al. (2004)
60			1.56	26			Barthold et al. (2004)
60	0.36	58	1.57	80			Garagorri et al. (2008)
60—90	0.3	21					Sir-Petermann et al. (2006)
75—105			0.95	409			Main et al. (2006)
80			0.81	113			Pierik et al. (2009)
90			0.95	598			Mau et al. (2007)
90			1.16	15			Andersson et al. (1998)
90			0.97 (F)	100			Bay et al. (2007)
90			0.91 (D)	51			Bay et al. (2007)
90			0.79	52			Cavarzere et al. (2010)
90			0.96	514			Boisen et al. (2005)
90			0.93	270			Boas et al. (2006)
90	0.30	58	1.23	80			Garagorri et al. (2008)
120	0.21	58	0.81	80			Garagorri et al. (2008)
180	0.13	58	0.19	80			Garagorri et al. (2008)
180			0.03	52			Cavarzere et al. (2010)

F = Finnish; D = Danish.

androgens produced by their male co-twin and may develop, for instance, male type behaviour (Tapp et al., 2011).

Maternal samples

Kerlan et al. (1994) have measured testosterone concentrations longitudinally during gestation and reported mildly increasing concentrations until birth and a decline post partum (**Figure 4A** and **Table 8**. These findings are consistent with those reported by Hohlagschwandtner et al. (2001) and Schubring et al. (1998). Maternal serum testosterone concentrations showed no fetal gender-related differences (Carlsen et al., 2005; Gol et al., 2004; Tuutti et al., 2011; van de Beek et al., 2004, 2009), but black mothers have higher concentrations compared with white mothers (Troisi et al., 2003b).

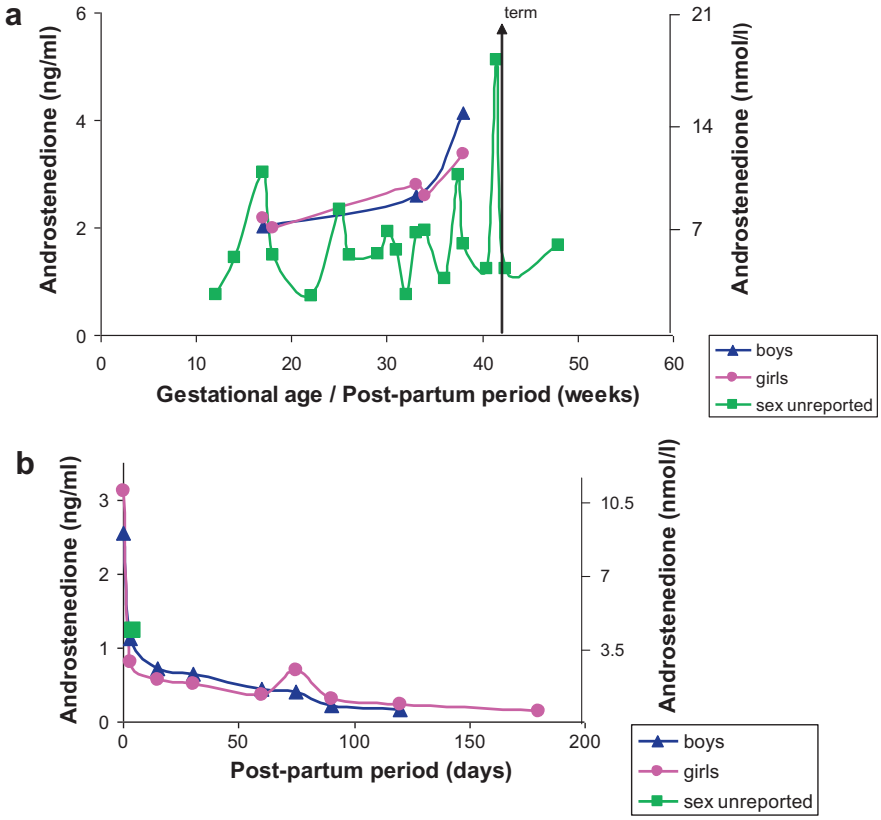

Figure 6 Weighted means of the reported maternal (**a**) and fetal and neonatal (**b**) serum androstenedione concentrations during gestation, at term and in the post-partum period.

Data from Gol et al. (2004) were much higher compared with all other studies. However, comparing this study to Troisi et al. (2003c), done at about the same gestational age showed that the comparable methods used (both radioimmunoassay, coefficients of variation are the same) and more importantly the oestradiol concentrations did not differ very much. The high testosterone concentrations found by Gol et al. (2004) could not be explained.

Amniotic fluid testosterone concentrations rise slowly between 14 and 22 weeks of gestation (**Figure 4B** and **Table 8**), with significantly higher concentrations in mothers pregnant with a male compared with a female fetus (Anand-Ivell et al., 2008; Auyeung et al., 2009; van de Beek et al., 2004, 2009). However, in amniotic fluid as well as saliva, overall testosterone concentrations were lower compared with serum concentrations (Anand-Ivell et al., 2008; Auyeung et al., 2009; Marrs et al., 2007; van de Beek et al., 2004, 2009).

Fetal/neonatal samples

Tremendous variation in cord blood testosterone was reported (**Figure 5** and **Table 9**). For girls values vary between 0.19 and 3712.7 ng/ml, and for boys between 0.14 and 252 ng/ml (Anderson et al., 2010; Barthold et al., 2004; Bay et al., 2007; Bergada et al., 2006; Boas et al., 2006; Boisen et al., 2005; Cavarzere et al., 2010; Forest et al., 1974; Garagorri et al., 2008; Gol et al., 2004; Hickey et al., 2010; Lahlou et al., 2004; Maccoby et al., 1979; Main et al., 2006; Mau et al., 2007; Pierik et al., 2009; Simmons, 1995; Troisi et al., 2003b,c; van de Beek et al., 2004; Whitehouse et al., 2010). Data presented by Gol et al. (2004) and Whitehouse et al. (2010) showed much higher testosterone concentrations compared with other studies and are therefore not included in **Figure 5**. Whitehouse et al. (2010) reported high cord blood testosterone concentrations in females (3712.7 ng/ml) but they claim to show comparable results to Troisi et al. (2003b); 0.16 ng/ml). From the paper it is not entirely clear which unit is used for testosterone. Within the text they refer to testosterone as nmol/l but all other testosterone measurements are in pmol/l. However, if they used pmol/l instead of nmol/l they would still report higher testosterone concentrations (3.7 ng/ml) compared with Troisi et al. (2003b) and all others as well. Data presented by Gol et al. (2004) showed higher testosterone concentrations for both maternal serum and umbilical cord blood. Assays used were comparable and could not account for this difference (Gol et al., 2004). Whether cord blood samples differ significantly between the sex (Garagorri et al., 2008; Troisi et al., 2003b) or not (Gol et al., 2004; van de Beek et al., 2004) remains debatable. However, neonatal data from 2 days after birth until 6 months of age are more consistent with significantly higher testosterone concentrations in boys compared with girls (Bergada et al., 2006; Garagorri et al., 2008). As demonstrated in **Figure 5**, for both girls and boys testosterone concentrations increase shortly after birth. Thereafter, for girls concentrations

Table 10 Maternal serum androstenedione concentrations during gestation and post partum.

	Girls		*Boys*		*Sex unreported*		*Study*
	Androstenedione (ng/ml)	n	*Androstenedione (ng/ml)*	n	*Androstenedione (ng/ml)*	n	
Gestational age (weeks)							
12					0.77	51	Soldin et al. (2005)
14					1.45	10	Kerlan et al. (1994)
15–18	1.55	78	1.41	75			van de Beek et al. (2004)
17					3.04	147	Carlsen et al. (2006)
17	2.95	63	2.66	71			Carlsen et al. (2005)
18	2	118					Hickey et al. (2010)
18					1.5	10	Kerlan et al. (1994)
22					0.75	50	Soldin et al. (2005)
22					1.55	10	Kerlan et al. (1994)
25					2.35	63	Carlsen et al. (2010)
26					1.5	10	Kerlan et al. (1994)
28–29					1.52	303	Janzen et al. (2007)
28–32					2.1	20	Serin et al. (2001)
30					1.55	10	Kerlan et al. (1994)
30–31					1.58	401	Janzen et al. (2007)
30–35	1.4	78	1.3	75			van de Beek et al. (2004)
32					0.76	50	Soldin et al. (2005)
32–34					1.37	764	Janzen et al. (2007)
33					4.78	143	Carlsen et al. (2006)
33	4.5	64	4	70			Carlsen et al. (2005)
34					1.95	10	Kerlan et al. (1994)
34	2.6	114					Hickey et al. (2010)
35–36					1.06	702	Janzen et al. (2007)
37–38					2.76	86	Troisi et al. (2003d)
37–38					3.23	86	Troisi et al. (2003a)
38	3.59	86	4.54	86			Troisi et al. (2003c)
38	3.14	86	3.74	86			Troisi et al. (2003b)
38					1.7	10	Kerlan et al. (1994)
41–42					5.13	489	Carlsen and Heimstad (2011)
Post partum (days)							
4					1.25	10	Kerlan et al. (1994)
42					1.68	20	Serin et al. (2001)

remain fairly constant, but for boys a second rise occurs at about 3 months after birth, the so-called mini-puberty (Andersson et al., 1998; Tomlinson et al., 2004).

Androstenedione

Androstenedione or 4-androstenedione is a steroid hormone produced in both the gonads and the adrenal glands. Adrenocorticotrophic hormone stimulates the production of adrenal androstenedione, whereas production of gonadal androstenedione is controlled by gonadotrophins. Androstenedione is the common precursor of testosterone and the oestrogens; oestrone and oestradiol. The enzyme 17β-hydroxysteroid dehydrogenase converts androstenedione to testosterone, while conversion to oestrogen requires the enzyme aromatase. In pre-menopausal women, the adrenal glands and ovaries each produce about 50% of the total androstenedione amount; therefore its production is about halved after menopause (Speroff and Fritz, 2005).

Maternal serum androstenedione concentrations during pregnancy have been linked to nausea, fetal size, duration of gestation and onset of labour (Jaffe, 1983; Norwitz et al., 1999). Furthermore, elevated first-trimester androstenedione is associated with development of pregnancy-induced hypertension or pre-eclampsia (Carlsen et al., 2005; Norwitz et al., 1999) and with a change in digit ratio (2D:4D) (Hickey et al., 2010).

Maternal samples

As demonstrated in **Figure 6A** and **Table 10**, androstenedione concentrations in maternal serum rise in women pregnant with a male or female fetus, but seem to fluctuate when gender is not taken into account (Carlsen et al., 2005, 2006, 2010; Carlsen and Heimstad, 2011; Hickey et al., 2010; Janzen et al., 2007; Kerlan et al., 1994; Ser-

Table 11 Fetal/neonatal serum androstenedione concentrations.

Post partum (days)	*Girls*		*Boys*		*Sex unreported*		*Study*
	Androstenedione (ng/ml)	n	*Androstenedione (ng/ml)*	n	*Androstenedione (ng/ml)*	n	
0	3.54	86	3.68	86			Troisi et al. (2003c)
0	3.21	86	3.4	86			Troisi et al. (2003b)
0	0.891	52	0.945	58			Maccoby et al. (1979)
0	5.58	82					Hickey et al. (2010)
0	1.46	14	1.28	7			Anderson et al. (2010)
0	2.14	58	2.23	80			Garagorri et al. (2008)
0	0.93	20	0.85	22			Forest et al. (1974)
3	0.81	58	1.13	80			Garagorri et al. (2008)
4					1.25	10	Kerlan et al. (1994)
15	0.58	58	0.72	80			Garagorri et al. (2008)
30	0.51	58	0.65	80			Garagorri et al. (2008)
60	0.37	58	0.44	80			Garagorri et al. (2008)
60–90	0.7	21					Sir-Petermann et al. (2006)
90	0.32	58	0.40	80			Garagorri et al. (2008)
120	0.25	58	0.22	80			Garagorri et al. (2008)
180	0.14	58	0.16	80			Garagorri et al. (2008)

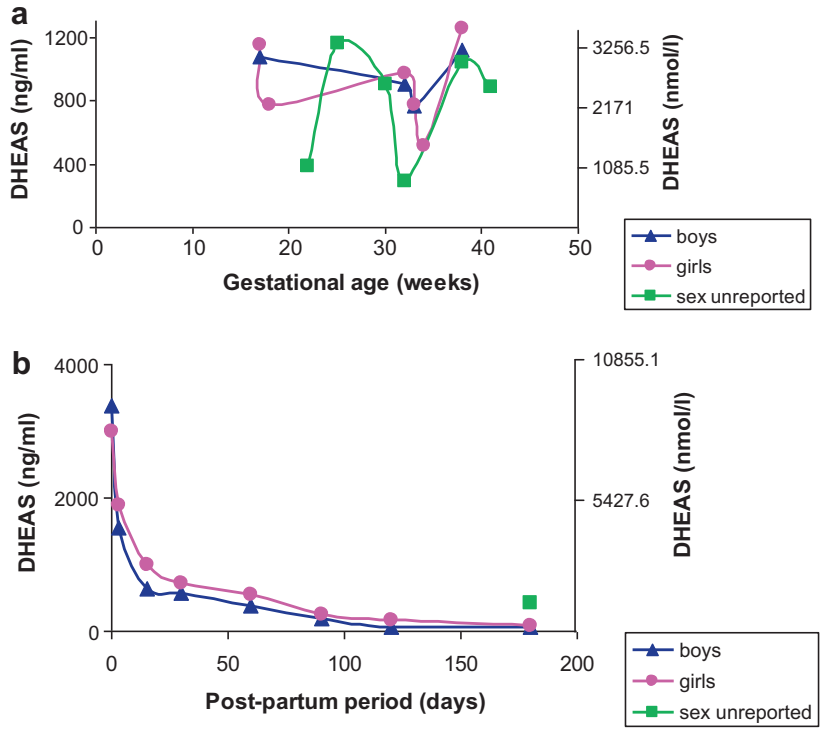

Figure 7 Weighted means of all reported maternal (**a**) and fetal and neonatal (**b**) serum dehydroepiandrosterone sulphate (DHEAS) concentrations during gestation, at term and in the post-partum period. Data from Gol et al. (2004) are not included.

in et al., 2001; Soldin et al., 2005; Troisi et al., 2003a,b,c,d; van de Beek et al., 2004). No sex-related differences were observed (Troisi et al., 2003b,c; van de Beek et al., 2004). Ethnical discordance however, has been reported by Troisi et al. (2003b), who demonstrated higher androstenedione concentrations in black mothers compared with white mothers. Amniotic fluid androstenedione concentrations are significantly higher in women pregnant with a male (0.71 ng/ml) compared with a female (0.45 ng/ml) fetus (van de Beek et al.,

Table 12 Maternal serum DHEAS concentrations during gestation.

Gestational age (weeks)	*Girls*		*Boys*		*Sex unreported*		*Study*
	DHEAS (ng/ml)	n	*DHEAS (ng/ml)*	n	*DHEAS (ng/ml)*	n	
15–18	1256.6	78	1186.5	75			van de Beek et al. (2004)
17	1031.8	63	958.1	71			Carlsen et al. (2005)
18	773.8	118					Hickey et al. (2010)
22					388.1	50	Soldin et al. (2005)
25					1160.7	63	Carlsen et al. (2010)
28–32					905	20	Serin et al. (2001)
30–35	976.5	78	906.5	75			van de Beek et al. (2004)
32					294.8	50	Soldin et al. (2005)
33	773.8	63	700.1	71			Carlsen et al. (2005)
34	519.6	114					Hickey et al. (2010)
37–38					690	86	Troisi et al. (2003d)
37–38					1390	86	Troisi et al. (2003a)
37–39	76,100	31	94,000	29			Gol et al. (2004)
38	1260	86	1120	86			Troisi et al. (2003c)
41–42					884.4	489	Carlsen and Heimstad (2011)

DHEAS = dehydroepiandrosterone sulphate.

Table 13 Fetal/neonatal serum DHEAS concentrations.

Post partum (days)	*Girls*		*Boys*		*Study*
	DHEAS (ng/ml)	n	*DHEAS (ng/ml)*	n	
0	5774.2	78	6091.1	75	Van de Beek et al. (2004)
0	192,200	31	220,700	29	Gol et al. (2004)
0	2217.4	58	2087.2	80	Garagorri et al. (2008)
0	1970	86	2210	86	Troisi et al. (2003c)
0	2210.9	82			Hickey et al. (2010)
3	1898.9	58	1552.2	80	Garagorri et al. (2008)
15	998.4	58	631	80	Garagorri et al. (2008)
30	717.6	58	564.8	80	Garagorri et al. (2008)
60	547.4	58	388	80	Garagorri et al. (2008)
90	262.2	58	194.3	80	Garagorri et al. (2008)
120	178.4	58	54.3	80	Garagorri et al. (2008)
180	80.1	58	67.1	80	Garagorri et al. (2008)

DHEAS = dehydroepiandrosterone sulphate.

2004). However, overall amniotic fluid concentrations are lower compared with serum.

Fetal/neonatal samples

Reported cord blood androstenedione concentrations show a wide range and higher concentrations are reported for girls (Anderson et al., 2010; Forest et al., 1974) as well as for boys (Garagorri et al., 2008; Maccoby et al., 1979; Troisi et al., 2003b,c). None of these differences were significant with the exception of female neonates of mothers with PCOS who have lower androstenedione concentrations compared with controls (Anderson et al., 2010). Unlike maternal samples, racial differences were not found for cord blood hormones (Troisi et al., 2003b). Overall, as demonstrated in **Figure 6B** and **Table 11**, neonatal androstenedione concentrations decrease from birth into childhood (Anderson et al., 2010; Forest et al., 1974; Garagorri et al., 2008;

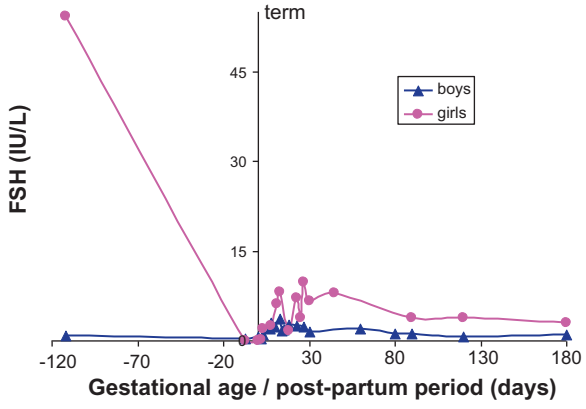

Figure 8 Weighted means of all reported fetal and neonatal serum FSH concentrations during gestation, at term and in the post-partum period. Data from Greaves et al. (2008) on premature births are not included.

Table 14 Fetal/neonatal serum FSH concentrations.

	Girls		*Boys*		*Study*
FSH (IU/l)	n	*FSH (IU/l)*	n		
Gestational age (weeks)					
24	54.4	11	0.77	14	Debieve et al. (2000)
39	Undetectable	11	0.33	12	Debieve et al. (2000)
Post partum (days)					
0	0.06	15	0.7	15	Andersson et al. (1998)
0 (gestational age 24–29)	6.3	6	1.9	14	Greaves et al. (2008)
1–5	2.0	31	0.96	30	Schmidt and Schwarz (2000)
1–30			0.2–3.5	215	Lahlou et al. (2004)
2	0.17	13	0.25	57	Bergada et al. (2006)
3–43 (gestational age 24–29)	54.6	15	1.1	15	Greaves et al. (2008)
6–10	2.44	17	2.91	15	Schmidt and Schwarz (2000)
7			2.04	57	Bergada et al. (2006)
7–14	6.09	14			Bergada et al. (2002)
10			2.3	57	Bergada et al. (2006)
11–15	8.16	8	3.71	17	Schmidt and Schwarz (2000)
14			1.73	57	Bergada et al. (2006)
16–20	1.62	6	2.63	14	Schmidt and Schwarz (2000)
20			1.31	57	Bergada et al. (2006)
21–25	7.07	3	2.5	7	Schmidt and Schwarz (2000)
21–28	3.87	10			Bergada et al. (2002)
26–28	9.74	8	2.25	8	Schmidt and Schwarz (2000)
30	6.65	13	1.48	57	Bergada et al. (2006)
30			1.4	52	Cavarzere et al. (2010)
30–90			0.2–4	215	Lahlou et al. (2004)
35–56	7.9	7			Bergada et al. (2002)
60			1.3	26	Barthold et al. (2004)
60–90	5.4	21			Sir-Petermann et al. (2006)
75–105			1.21 (D)	409	Main et al. (2006)
75–105			1.33 (F)	318	Main et al. (2006)
80			1.1	113	Pierik et al. (2009)
90	2.57	15	1.79	15	Andersson et al. (1998)
90			1.15	514	Boisen et al. (2005)
90			1.2	598	Mau et al. (2007)
90	3.8			325	Chellakooty et al. (2003)
90			2	52	Cavarzere et al. (2010)
120	3.8	10	0.7	7	Ibanez et al. (2002)
180	3.05	15	0.96	15	Andersson et al. (1998)

D = Danish; F = Finnish.

Hickey et al., 2010; Kerlan et al., 1994; Maccoby et al., 1979; Sir-Petermann et al., 2006; Troisi et al., 2003b,c).

DHEAS

DHEAS is produced mainly by the adrenal gland, but little is produced in the gonads as well. It is derived from cholesterol via pregnenolone and 17-α-hydroxypregnolone. Dehydroepiandrosterone is converted to its sulphated form DHEAS in the liver, adrenals and small intestine (Speroff and Fritz, 2005).

During gestation, DHEAS is the major source of oestriol production in the fetal–placental unit (Speroff and Fritz, 2005; Tagawa et al., 2004). Maternal DHEAS production rises while serum concentrations are lower compared with non-pregnant women, which could be the result of conversion to oestrogens (Tagawa et al., 2004). Administration of DHEAS to assess placental function was performed in the 1970s and 1980s. The amount of oestrogens produced after DHEAS administration was said to be an expression of fetal well being (Bazsa-Kassai et al., 1985; Tulchinsky et al., 1976).

Maternal samples

Fluctuating DHEAS concentrations for girls and boys have been demonstrated during gestation (**Figure 7A** and

Table 12; Carlsen and Heimstad, 2011; Carlsen et al., 2005, 2010; Gol et al., 2004; Hickey et al., 2010; Serin et al., 2001; Soldin et al., 2005; Troisi et al., 2003a,c,d; van de Beek et al., 2004). Tagawa et al. (2004) have reported a decline in DHEAS concentrations during pregnancy, while after delivery concentrations returned quickly to pre-gestational concentrations. Only two papers actually compared fetal gender and reported no differences between women pregnant with a boy or a girl (Gol et al., 2004; van de Beek et al., 2004). In accordance with testosterone, data by Gol et al. (2004) again demonstrated values that are much higher compared with the other papers. Amniotic fluid values reported by Torricelli et al. (2009); 0.17 ng/ml, gestational age 16 weeks) are lower compared with van de Beek et al. (2004); 313.2 ng/ml, gestational age 15—18 weeks), which are comparable to serum concentrations.

Fetal/neonatal samples

Cord blood DHEAS concentrations are high; some report significantly higher concentrations in girls (Garagorri et al., 2008), while others did not confirm any gender-related differences (Gol et al., 2004; van de Beek et al., 2004). Data from Gol et al. (2004), as already mentioned, do not correspond with the data reported in the other studies. In the post-natal period, DHEAS concentrations drop and reach their minimum at about 3 months of age and remain stable afterwards (**Figure 7B** and **Table 13**; Garagorri et al., 2008; Gol et al., 2004; Hickey et al., 2010; Serin et al., 2001; Tagawa et al., 2004; Troisi et al., 2003c; van de Beek et al., 2004).

FSH

FSH is a glycoprotein, consisting of an alpha- and a beta-subunit. The beta-subunit is unique while FSH shares its alpha-subunit with LH, thyroid-stimulating hormone and human chorionic gonadotrophin. Therefore, the beta-subunit is responsible for interaction with the FSH receptor. In women FSH stimulates follicle growth, and in males FSH interacts with the Sertoli cells to stimulate spermatogenesis.

Early follicular-phase FSH concentrations are often used in infertility patients to predict ovarian reserve, often combined with antral follicle count and AMH (Broekmans et al., 2006). When focusing on assisted reproduction, basal FSH values probably predict quantitative rather than qualitative results (Fourati et al., 2012).

Maternal samples

Maternal serum FSH concentrations during gestation are stable and almost undetectable (around 0.5 IU/l), which is probably due to excessive oestrogen production by the placenta (Fowler et al., 1998).

Fetal/neonatal samples

Fetal samples taken, during gestation, from the umbilical cord (gestational age 24 weeks) demonstrated high FSH concentrations in girls (54.4 IU/l) and much lower concentrations in boys (0.77 IU/l), which is in contrast to samples taken at term (gestational age 39 weeks) where boys drop to 0.33 IU/l while in girls FSH is undetectable (Debieve et al., 2000). In cord blood samples or those taken within a week after birth, higher FSH concentrations are reported for boys compared with girls (Andersson et al., 1998; Bergada et al., 2006). Hereafter, this relationship inverses and girls remain to have higher FSH concentrations until puberty (Andersson et al., 1998; Bergada et al., 2006; Ibanez et al., 2002). Overall, neonatal FSH concentrations fluctuate in the post-partum period (**Figure 8** and **Table 14**); however, for both sexes, but most explicit in girls, a peak is shown at about 40—60 days post partum (Andersson et al., 1998; Barthold et al., 2004; Bergada et al., 2002, 2006; Boisen et al., 2005; Cavarzere et al., 2010; Chellakooty et al., 2003; Ibanez et al., 2002; Lahlou et al., 2004; Main et al., 2006; Mau et al., 2007; Schmidt and Schwarz, 2000). Greaves et al. (2008) have collected data (cord blood and neonatal serum) from children born between 24 and 29 weeks of gestation. Cord blood samples of these premature children showed much higher FSH concentrations (males mean gestational age 28 weeks: 1.9 IU/l; females mean gestational age 27 weeks: 6.3 IU/l; Greaves et al., 2008) compared with those demonstrated at term by Andersson et al. (1998). After 3 weeks, serum FSH had lowered in the premature born boys (1.1 IU/l) but increased dramatically in these girls (54.6 IU/l). This confirms earlier data reporting the same rebound effect in prematurely born girls (Tapanainen et al., 1981).

LH

LH is a heterodimeric glycoprotein produced by the anterior pituitary gland. In accordance to FSH, it shares its alpha-subunit with other glycoproteins while its unique beta-subunit binds the LH receptor. In women, LH has its most profound effect during the LH surge which precedes the ovulation. LH concentrations are normally low during childhood and very high in post-menopausal women. In males, Leydig cells of the testis are stimulated by LH to produce testosterone (Speroff and Fritz, 2005).

Maternal samples

Although maternal serum LH concentrations during gestation increase rapidly to a maximum of 3 IU/l in the first

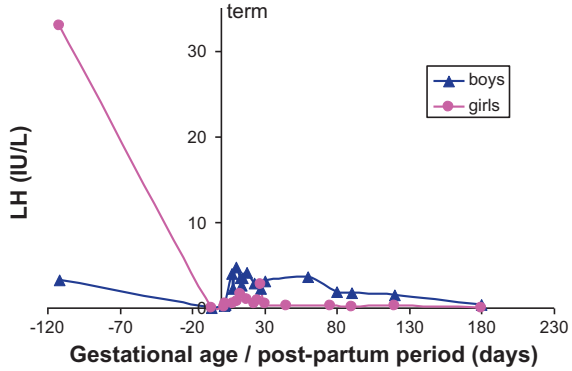

Figure 9 Weighted means of all reported fetal and neonatal serum LH concentrations during gestation, at term and in the post-partum period. Data from Greaves et al. (2008) on premature births are not included.

Table 15 Fetal/neonatal serum LH concentrations.

	Girls		*Boys*		*Study*
LH (IU/l)	n	*LH (IU/l)*	n		
Gestational age (weeks)					
24	33	11	3.3	14	Debieve et al. (2000)
39	Undetectable	11	Undetectable	12	Debieve et al. (2000)
Post partum (days)					
0 (gestational age 24–29)	1.8	6	5.2	14	Greaves et al. (2008)
1–5	0.48	31	0.39	30	Schmidt and Schwarz (2000)
1–30			0.5–6.5	215	Lahlou et al. (2004)
2	0.1	13	0.21	57	Bergada et al. (2006)
3–43 (gestational age 24–29)	13.9	21	1.7	25	Greaves et al. (2008)
6–10	0.45	17	2.31	15	Schmidt and Schwarz (2000)
7			3.94	57	Bergada et al. (2006)
7–14	0.78	14			Bergada et al. (2002)
10			4.81	57	Bergada et al. (2006)
11–15	1.58	8	3.55	17	Schmidt and Schwarz (2000)
14			2.64	57	Bergada et al. (2006)
16–20	1.03	6	4.13	14	Schmidt and Schwarz (2000)
20			2.67	57	Bergada et al. (2006)
21–25	0.46	3	2.86	7	Schmidt and Schwarz (2000)
21–28	0.84	10			Bergada et al. (2002)
26–28	2.75	8	2.22	8	Schmidt and Schwarz (2000)
30			3.3	52	Cavarzere et al. (2010)
30	0.49	13	2.95	57	Bergada et al. (2006)
30–90			0.5–7.1	215	Lahlou et al. (2004)
35–56	0.24	7			Bergada et al. (2002)
60			2.6	26	Barthold et al. (2004)
60–90	0.3	21			Sir-Petermann et al. (2006)
75–105			1.77	409	Main et al. (2006)
80			1.9	110	Pierik et al. (2009)
90			1.63 (F)	51	Bay et al. (2007)
90			1.67 (D)	100	Bay et al. (2007)
90	0.08	15	1.74	15	Andersson et al. (1998)
90			1.7	514	Boisen et al. (2005)
90			2.8	52	Cavarzere et al. (2010)
90	0.07	324			Chellakooty et al. (2003)
90			1.7	598	Mau et al. (2007)
120	0.2	10	1.5	7	Ibanez et al. (2002)
180	<0.05	15	0.36	15	Andersson et al. (1998)

D = Danish; F = Finnish.

trimester and slowly decline until birth, these are still almost hypogonadal values (around 0.5 IU/l) (Fowler et al., 1998).

Fetal/neonatal samples

Fetal samples taken *in utero*, from the umbilical cord (gestational age 24 weeks) demonstrated high LH concentrations in girls (33 IU/l) and much lower concentrations in boys (3.3 IU/l), while in samples taken at term (gestational age 39 weeks) LH was undetectable, irrespective of fetal gender (Debieve et al., 2000). Cord blood samples are only available for premature births (gestational age 24–29 weeks). Greaves et al. (2008) showed higher LH concentrations in males (mean gestational age 28 weeks, 5.2 IU/l) versus females (mean gestational age 27 weeks, 1.8 IU/l). After 3 weeks serum LH concentrations in boys had diminished (1.7 IU/l) but, in accordance with FSH, LH in these girls showed a drastic rise (13.9 IU/l), again confirming data by Tapanainen et al. (1981). Overall, serum LH was low shortly after birth but had a remarkable increment from day 7 throughout the first month, this was more explicit in males but present in females as well (**Figure 9** and **Table 15**; Bergada et al., 2002, 2006). Until 3 months of age, diminishing LH concentrations are reported by Cavarzere et al. (2010) and Bergada et al. (2002). The mini-puberty, at about 3–4

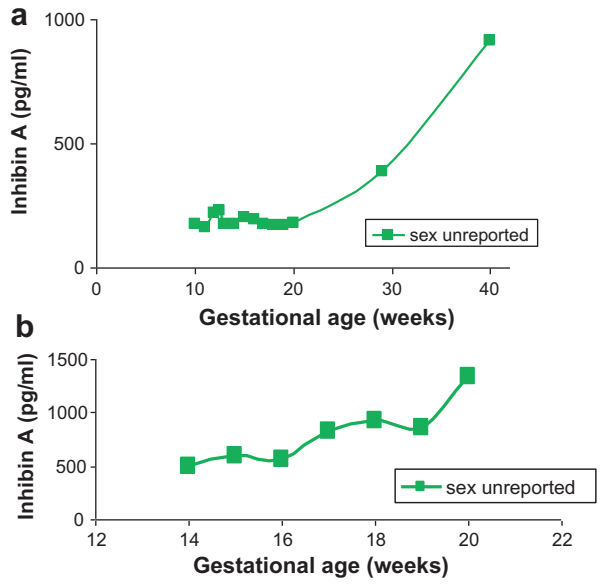

Figure 10 Weighted means of all reported maternal serum (**a**) and amniotic fluid (**b**) inhibin A concentrations during gestation. Fetal sex is unreported for all measurements.

months in which hormone concentrations rise, reported by Andersson et al. (1998), is not confirmed by these data. After 3 months, decreasing LH concentrations are reported for both sexes. Neonatal samples from term-born females indicate significantly lower LH concentrations compared with males (Andersson et al., 1998; Bergada et al., 2006; Ibanez et al., 2002).

Inhibins

Inhibin is a dimeric disulphide-linked glycoprotein consisting of two subunits (alpha and beta) and is part of the transforming growth factor β protein family. All inhibins share a common alpha-subunit, depending on the type of beta-subunit; inhibin is classified as inhibin A or B. The main role of inhibin is the down-regulation of FSH synthesis (Speroff and Fritz, 2012). In women, inhibin is produced by the ovary, the pituitary and the placenta. Inhibin A is derived from the dominant follicle and the corpus luteum and inhibin B is produced in the small antral follicles in the ovary (Muttukrishna, 2004).

Within the testes, FSH stimulates Sertoli cells to produce inhibin B, which in turn negatively feeds back on the hypothalamus. It also facilitates LH-stimulated testosterone production by Leydig cells. Inhibin B is widely used in subfertile males as a marker for spermatogenesis (Speroff and Fritz, 2005).

During pregnancy, inhibin A is produced by the placenta and fetal membranes and is the predominant form of inhibin in maternal serum (Muttukrishna, 2004; Wallace et al., 1997). Inhibin A is part of the prenatal screening used to identify fetuses affected by Down's syndrome (Lam and Tang, 1999; Wallace et al., 1996, 1999), but abnormal concentrations have also been associated with miscarriage, preterm labour and pre-eclampsia (Reddy et al., 2009; Spencer et al., 2008).

Inhibin A: maternal samples

Overall, maternal serum inhibin A rises during gestation with the highest concentrations found at term (**Figure 10A** and **Table 16**; Fowler et al., 1998; Muttukrishna, 2004; Plevyak et al., 2003). However, a gradual decline from 10 to 16 weeks of gestation has been reported (Phupong et al., 2008) and thereafter data show conflicting outcomes (Davidson et al., 2003; Lam and Tang, 1999; Muttukrishna, 2004; Wallace et al., 1996). Maternal serum inhibin A concentrations are lower compared with those measured in amniotic fluid at similar gestational ages (**Figure 10B** and **Table 16**; Davidson et al., 2003; Wallace et al., 1996, 1998, 1999).

Inhibin A: fetal/neonatal samples

Neonatal inhibin A data were only available for girls and demonstrated a rapid decline from 79 pg/ml in the first week to almost undetectable at about 3 months of age (**Figure 11** and **Table 17**).

Inhibin B: maternal samples

Limited data are available on inhibin B concentrations in maternal serum during pregnancy. Petraglia et al. (1997) have shown a plateau (30 pg/ml) until approximately 28 weeks followed by an increase up until birth (between 100–150 pg/ml). Shortly after birth, inhibin B concentrations decline rapidly until the plateau is reach again after approximately 12 h (Petraglia et al., 1997). These findings are confirmed by Fowler et al. (1998). Two papers by the same research group reported on amniotic fluid inhibin B, which partly contained the same population. Increasing inhibin B concentrations between 14 and 20 weeks of gestation have been reported in both studies, but this is much more explicit in the second publication (**Figure 12** and **Table 18**; Wallace et al., 1998; Wallace et al., 1999). Moreover, amniotic fluid samples contain much higher inhibin B concentrations compared with serum samples.

Inhibin B: fetal/neonatal samples

Fetal samples taken *in utero*, from the umbilical cord at 24 weeks of gestation demonstrated significantly higher inhibin B concentrations in boys (167.6 pg/ml) compared with girls (16.4 pg/ml). In samples taken at term (gestational age 39 weeks), inhibin B was undetectable in girls and 125.3 pg/ml in boys (Debieve et al., 2000). Andersson et al. (1998) reported cord blood inhibin B data which were very low in girls and much higher in boys, but no statistical analysis was done to compare these outcomes. Overall, neonatal serum inhibin B concentrations seem to rise from birth to at about 1 month of age (Andersson et al., 1998; Bergada et al., 2006; Cavarzere et al., 2010; Lahlou et al., 2004) and then drop drastically (**Figure 13** and **Table 19**). Thereafter in boys concentrations rise again, whereas in girls the decline continues. Boys in the first 6 months of life show significantly higher inhibin B concentrations compared with girls (Bergada et al., 2002; Chellakooty et al., 2003; Ibanez et al., 2002), which even exceed those found in adult males (Andersson et al., 1998; Bergada et al., 2006; Ibanez et al., 2002). Most studies reporting on inhibin B in boys at one particular time point indicate comparably high neonatal serum concentrations (Barthold et al., 2004; Boisen et al., 2005; Cavarzere et al., 2010; Crofton et al., 2002; Main et al.,

Table 16 Maternal serum and amniotic fluid inhibin A concentrations during gestation.

Gestational age (weeks)	*Sex unreported*		*Study*
	Inhibin A (pg/ml)	n	
Maternal serum			
10	177.5	75	Wallace et al. (1997)
11	164.3	75	Wallace et al. (1997)
11—14	231	240	Spencer et al. (2008)
12	355	36	Phupong et al. (2008)
12	159.1	75	Wallace et al. (1997)
13	268	33	Phupong et al. (2008)
13	133.9	75	Wallace et al. (1997)
14	255	19	Phupong et al. (2008)
14	157.4	75	Wallace et al. (1997)
15	282	36	Lam and Tang (1999)
15	237	45	Wallace et al. (1996)
15	142.5	75	Wallace et al. (1997)
15—20	188	155	Davidson et al. (2003)
16	210	95	Lam and Tang (1999)
16	267	55	Wallace et al. (1996)
16	119.2	75	Wallace et al. (1997)
17	203	114	Lam and Tang (1999)
17	207	50	Wallace et al. (1996)
17	111.9	75	Wallace et al. (1997)
18	191	62	Lam and Tang (1999)
18	156.0	75	Wallace et al. (1997)
19	233	34	Lam and Tang (1999)
19	146.2	75	Wallace et al. (1997)
20	180.3	57	Wallace et al. (1997)
23—34	352	96	Plevyak et al. (2003), not in labour
23—34	443	65	Plevyak et al. (2003), in labour
37—42	872	65	Plevyak et al. (2003), not in labour
37—42	953	65	Plevyak et al. (2003), in labour
Amniotic fluid			
14	334	50	Wallace et al. (1999)
14	615	73	Wallace et al. (1997)
15	396	50	Wallace et al. (1999)
15	680.2	117	Wallace et al. (1997)
16	480	52	Wallace et al. (1999)
16	340	45	Wallace et al. (1998)
16	728.7	87	Wallace et al. (1997)
17	486	46	Wallace et al. (1998)
17	640	50	Wallace et al. (1999)
17	997.8	133	Wallace et al. (1997)
18	362	46	Wallace et al. (1998)
18	700	50	Wallace et al. (1999)
18	1195.9	137	Wallace et al. (1997)
19	695	38	Wallace et al. (1999)
19	593	24	Wallace et al. (1998)
19	1130.7	47	Wallace et al. (1997)
20	1336.0	9	Wallace et al. (1997)

2006; Mau et al., 2007; Pierik et al., 2009). When focusing on the post-natal data for boys only, **Figure 13** demonstrates two peaks, the first at about 15 days and the second at about 90 days after birth, which is in line with increased testicular size measured by ultrasound in young boys (Kuijper et al., 2008).

SHBG

SHBG (or sex steroid-binding globulin) is a glycoprotein that contains a binding site for both testosterone and oestradiol. It is produced mainly by the liver but SHBG gene expression has been identified in other tissues, such as the brain,

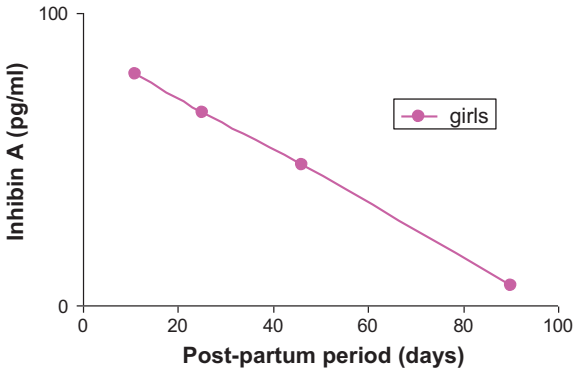

Figure 11 Weighted means of all reported neonatal serum inhibin A concentrations in the post-partum period in girls.

Table 17 Neonatal serum inhibin A concentrations in girls.

Post partum (days)	*Girls*		*Study*
	Inhibin A (pg/ml)	n	
7—14	79	14	Bergada et al. (2002)
21—28	65.8	10	Bergada et al. (2002)
35—56	47.9	7	Bergada et al. (2002)
90	<7	204	Chellakooty et al. (2003)

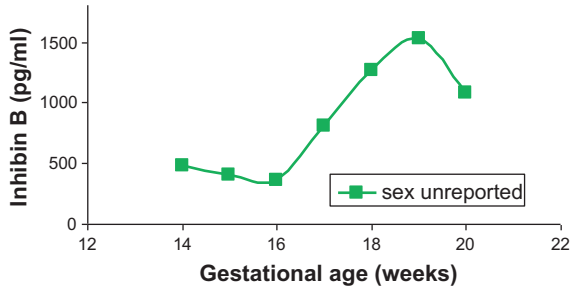

Figure 12 Weighted means of all reported amniotic fluid inhibin B concentrations during gestation.

Table 18 Amniotic fluid inhibin B concentrations during gestation.

Gestational age (weeks)	*Sex unreported*		*Study*
	Inhibin B (pg/ml)	n	
14	632	50	Wallace et al. (1999)
14	216.6	30	Wallace et al. (1997)
15	442	50	Wallace et al. (1999)
15	334.6	30	Wallace et al. (1997)
16	487	52	Wallace et al. (1999)
16	310	43	Wallace et al. (1998)
16	261.4	30	Wallace et al. (1997)
17	426	40	Wallace et al. (1998)
17	1212	50	Wallace et al. (1999)
17	631.8	30	Wallace et al. (1997)
18	450	40	Wallace et al. (1998)
18	2222	50	Wallace et al. (1999)
18	775.4	30	Wallace et al. (1997)
19	632	24	Wallace et al. (1998)
19	2439	38	Wallace et al. (1999)
19	1089.2	30	Wallace et al. (1997)
20	1078.2	9	Wallace et al. (1997)

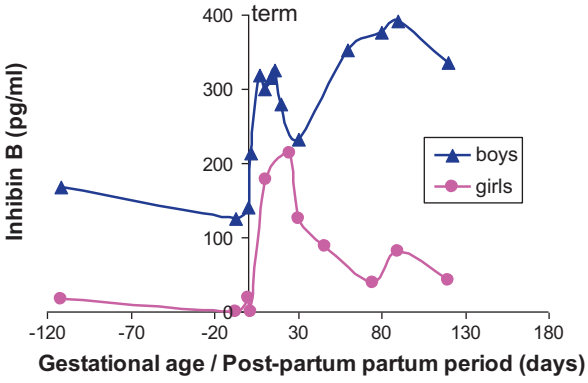

Figure 13 Weighted means of all reported fetal and neonatal serum inhibin B concentrations during gestation, at term and in the post-partum period.

placenta, testes and endometrium (Damassa and Cates, 1995). The amount of SHBG is increased in pregnancy, with hyperthyroidism and with oestrogen administration. On the other hand, lower SHBG concentrations have been associated with central obesity, raised blood pressure and insulin resistance in women with PCOS (Dong et al., 2012).

Preconception SHBG concentrations in women with PCOS are strongly associated with the development of gestational diabetes (Veltman-Verhulst et al., 2010). Low SHBG concentrations might even reflect insulin resistance better then fasting glucose or insulin (Smirnakis et al., 2007; Spencer et al., 2005). High insulin concentrations directly inhibit the hepatic SHBG production resulting in more bioavailable testosterone and oestradiol. Although, offspring size is said to be negatively associated with maternal androgen concentrations, no relationship between SHBG and birthweight has been found (Carlsen et al., 2006). Furthermore, low SHBG concentrations have also been found in first-trimester samples from women who miscarry (Spencer et al., 2005).

Maternal samples

Maternal serum SHBG concentrations increase during gestation and decline rapidly after birth, as demonstrated in **Figure 14A** and **Table 20** (Carlsen et al., 2006; Hickey et al., 2010; Kerlan et al., 1994; Lagiou et al., 2003; Mucci et al., 2003; Nelson et al., 2010; Schubring et al., 1998; Serin et al., 2001; Smirnakis et al., 2007; Spencer et al., 2005; van de Beek et al., 2004; Yu et al., 2004), and confirms data produced by Ekelund and Laurell (1994). No significant differences for SHBG concentrations in second- (15—18 weeks) or third- (30—35 weeks) trimester maternal serum samples between women pregnant with a male or female fetus were reported (van de Beek et al., 2004). Amniotic fluid samples taken between 15 and 18 weeks of gestation showed much lower SHBG concentrations compared with maternal serum

samples (male 8.69 /l; female 8.27 nmol/l; van de Beek et al., 2004).

Fetal/neonatal samples

Cord blood samples indicated no gender-related (van de Beek et al., 2004) or ethnical (Simmons, 1995) differences. Neonatal serum SHBG concentrations increase from birth to 3 months of age in both girls and boys (**Figure 14B** and **Table 21**; Barthold et al., 2004; Boas et al., 2006; Boisen et al., 2005; Chellakooty et al., 2003; Hickey et al., 2010; Main et al., 2006; Pierik et al., 2009; Simmons, 1995; Sir-Petermann et al., 2006; van de Beek et al., 2004). In contrast to serum values in adults, in neonatal samples no differences between neonates delivered by mothers with or without diabetes were found (Simmons, 1995).

AMH

AMH (or Müllerian inhibiting substance/factor) is a member of the transforming growth factor β family, which includes inhibin and activin. It is a homodimeric disulphide-linked glycoprotein. In the male fetus, AMH is synthesized by Sertoli cells (activated by SRY) soon after testicular differentiation and is essential for regression of the Müllerian ducts (Speroff and Fritz, 2005). AMH is detectable in the serum of males during infancy, childhood, adolescence and adulthood, but after puberty testosterone suppresses AMH secretion in males. The failure of testosterone to suppress AMH secretion during fetal and newborn life is explained by the absence of the androgen receptor in Sertoli cells until later in life (La Marca et al., 2005). The internal genitalia possess the intrinsic tendency to feminize. In the absence of a Y chromosome, functional testis and testosterone production the Wolffian system regresses. The lack of AMH allows retention of the Müllerian system and development of Fallopian tubes, uterus and upper vagina (Speroff and Fritz, 2005). In women, AMH is produced by the granulosa cells of the ovarian (pre-)antral follicles and appears to regulate early follicle development. In contrast to males, AMH is very low until puberty in females and is therefore used as a serum marker for ovarian reserve and ovarian ageing (Kwee et al., 2008).

Table 19 Fetal/neonatal serum inhibin B concentrations.

	Girls		*Boys*		*Study*
	Inhibin B (pg/ml)	n	*Inhibin B (pg/ml)*	n	
Gestational age (weeks)					
24	16.4	11	167.6	14	Debieve et al. (2000)
39	Undetectable	11	125.3	12	Debieve et al. (2000)
Post partum (days)					
0	<18	15	140	15	Andersson et al. (1998)
1—30			75—575	215	Lahlou et al. (2004)
0—365			278	51	Crofton et al. (2002)
2	0	13	214	57	Bergada et al. (2006)
7			319	57	Bergada et al. (2006)
7—14	177.2	14			Bergada et al. (2002)
10			300	57	Bergada et al. (2006)
14			316	57	Bergada et al. (2006)
20			280	57	Bergada et al. (2006)
21—28	213.9	10			Bergada et al. (2002)
30	125	13	361	57	Bergada et al. (2006)
30			89.5	52	Cavarzere et al. (2010)
30—90			125—570	215	Lahlou et al. (2004)
35—56	88.6	7			Bergada et al. (2002)
60			392.1	26	Barthold et al. (2004)
60—90	38.5	21			Sir-Petermann et al. (2006)
75—105			385 (D)	409	Main et al. (2006)
75—105			456 (F)	318	Main et al. (2006)
80			376.6	113	Pierik et al. (2009)
90			386	598	Mau et al. (2007)
90			389	514	Boisen et al. (2005)
90			141.7	52	Cavarzere et al. (2010)
90	82	324			Chellakooty et al. (2003)
120	58	10	280	7	Ibanez et al. (2002)
120	32	15	361	15	Andersson et al. (1998)

D = Danish; F = Finnish.

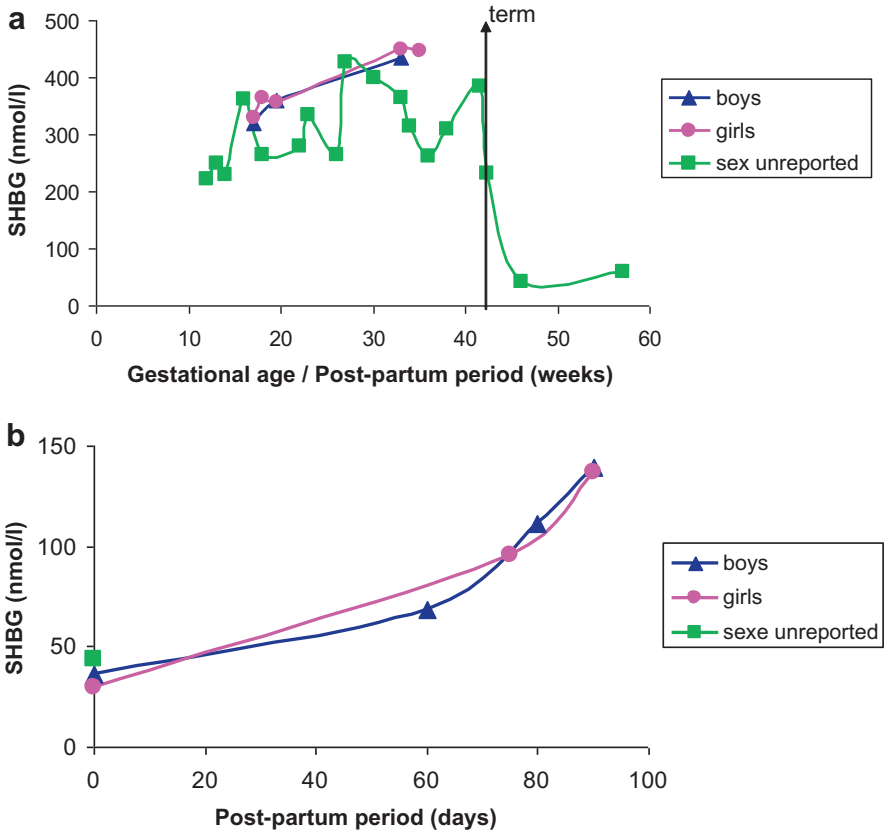

Figure 14 Weighted means of all reported maternal (**a**) and fetal and neonatal (**b**) serum SHBG concentrations during gestation, at term and in the post-partum period.

In assisted reproduction settings, AMH has been identified as a marker to predict women at risk for ovarian hyperstimulation syndrome (Ocal et al., 2011). Furthermore, AMH is associated with the number of mature oocytes retrieved during stimulation protocols in women with PCOS (Aleyasin et al., 2011) and is found useful in predicting treatment prognosis in women with elevated early follicular-phase FSH concentrations (Buyuk et al., 2011).

Maternal samples

Apart from at about 20 weeks, results indicate a decline in AMH in maternal serum during gestation (La Marca et al., 2005; Li et al., 2010; Nelson et al., 2010). Decline in AMH in maternal serum, whether this is significant (Li et al., 2010; Nelson et al., 2010) or not (La Marca et al., 2005), might be explained by group size, age distribution within the groups and study design. After birth, AMH rises quickly and reaches a plateau (**Figure 15A** and **Table 22**).

During pregnancy, the menstrual cycle is inactivated due to hormonal feedback and therefore, no follicles develop. This is in agreement with the reported diminished AMH production during gestation and the rise in AMH shortly after birth. When measuring AMH during pregnancy, as well as maternal age, one should take into account maternal body mass index (Nelson et al., 2010). For fetal gender, no differences have been observed (La Marca et al., 2005).

Fetal/neonatal samples

In cord blood, AMH concentrations in boys by far exceed those found in girls (Aksglaede et al., 2010; Hagen et al., 2010). As expected, serum AMH in male neonates rises until at about 3 months of age, whereafter concentrations decline to be almost undetectable at about 6 months of age (Bergada et al., 2006; Kuiri-Hanninen et al., 2011; Lahlou et al., 2004; Lee et al., 1996; Pierik et al., 2009; Sir-Petermann et al., 2006). In females, AMH is negligible in pre-pubertal ovaries (**Figure 15B** and **Table 23**). AMH is clearly age and gender specific from infancy to adulthood and can therefore be used as an early marker for testicular function (Bergada et al., 2006; Lee et al., 1996; Pierik et al., 2009).

Global overview

This review has tried to summarize all reported data into one graphical representation (**Figure 16**) demonstrating an interpretation of the hormonal changes that occur during gestation and post partum. Because this is only a rough estimate of the actual endocrine data, no scale or units have been added to this figure, rather they represent the course in time. However, the Y-axis should be seen as a logarithmic scale because oestrogens occur in concentrations that are orders of magnitude higher.

There is very limited information available on hormone exposure during twin pregnancies or in neonates who are born as part of a twin. This study's search resulted in four

Table 20 Maternal serum SHBG concentrations during gestation and post partum.

	Girls		*Boys*		*Sex unreported*		*Study*
	SHBG (nmol/l)	n	*SHBG (nmol/l)*	n	*SHBG (nmol/l)*	n	
Gestational age (weeks)							
12					207	60	Nelson et al. (2010)
12					225	400	Spencer et al. (2005)
13					250	400	Spencer et al. (2005)
14					230	10	Kerlan et al. (1994)
15—18	331	78	325	75			van de Beek et al. (2004)
16					364	270	Lagiou et al. (2006)
16					361	53	Lagiou et al. (2003)
16					362	230	Mucci et al. (2003)
17					320	73	Smirnakis et al. (2007)
17					320	147	Carlsen et al. (2006)
18	364	122					Hickey et al. (2010)
18					264	10	Kerlan et al. (1994)
19—20	357.9	91	360.3	91			Tuutti et al. (2011)
22					280	10	Kerlan et al. (1994)
22—24					336	602	Yu et al. (2004)
26					291	10	Kerlan et al. (1994)
26					261	60	Nelson et al. (2010)
27					426	270	Lagiou et al. (2006)
27					434	53	Lagiou et al. (2003)
27					426	230	Mucci et al. (2003)
28—32					452	20	Serin et al. (2001)
30					298	10	Kerlan et al. (1994)
33					366	145	Carlsen et al. (2006)
30—35	449	78	436	75			van de Beek et al. (2004)
34					315	10	Kerlan et al. (1994)
34—36	448	117					Hickey et al. (2010)
36					262	60	Nelson et al. (2010)
38					310	10	Kerlan et al. (1994)
41—42					386	489	Carlsen and Heimstad (2011)
Post partum (days)							
4					232	10	Kerlan et al. (1994)
42					43	20	Serin et al. (2001)
120					60	60	Nelson et al. (2010)

D = Danish; F = Finnish; SHBG = sex hormone-binding globulin.

articles reporting hormone concentrations in twin pregnancies (**Table 24**; Gonzalez et al., 1989; Sakai et al., 1991; Smith et al., 2009; Thomas et al., 1998). For oestrogens, significantly higher maternal serum (oestradiol and oestriol) and urine (oestriol) concentrations were found in twins compared with singletons (Gonzalez et al., 1989; Smith et al., 2009; Thomas et al., 1998). No differences in umbilical cord blood oestradiol concentrations were found for gender or zygosity in same-sex monozygotic and dizygotic twins (Sakai et al., 1991). Higher maternal serum testosterone concentrations were reported in twin pregnancies compared with mothers carrying a singleton (Thomas et al., 1998), as well as in boys of same-sex twins compared with girls of same-sex twins (Sakai et al., 1991).

Discussion

Hormones play an important part in defining the optimal conditions for human life to start. Up until now, there is a struggle to reliably measure and reproduce hormonal concentrations during gestation. Although, poor correlations between maternal samples and umbilical cord blood have been reported (Troisi et al., 2003c), measurements done in the mother (serum, amniotic fluid, saliva or urine) are often used as a substitute for fetal hormones. This still leaves one in the dark about the actual hormone concentrations affecting the developing fetus, but gender-specific development is said to be steroid hormone dependant (Carlsen et al., 2010; Cattrall et al., 2005; Ekelund and Laurell, 1994; Hohlagschwandtner et al., 2001; Iwata et al., 2011;

Table 21 Fetal/neonatal serum SHBG concentrations.

Post partum (days)	*Girls*		*Boys*		*Sex unreported*		*Study*
	SHBG (nmol/l)	n	*SHBG (nmol/l)*	n	*SHBG (nmol/l)*	n	
0	33.8	78	36.4	75			van de Beek et al. (2004)
0	26	82					Hickey et al. (2010)
0					44	125	Simmons (1995)
60			68.8	26			Barthold et al. (2004)
60—90	95.8	21					Sir-Petermann et al. (2006)
75—105			136 (D)	409			Main et al. (2006)
75—105			143 (F)	318			Main et al. (2006)
80			110.9	113			Pierik et al. (2009)
90			141	270			Boas et al. (2006)
90			138	514			Boisen et al. (2005)
90	137	319					Chellakooty et al. (2003)

D = Danish; F = Finnish; SHBG = sex hormone-binding globulin.

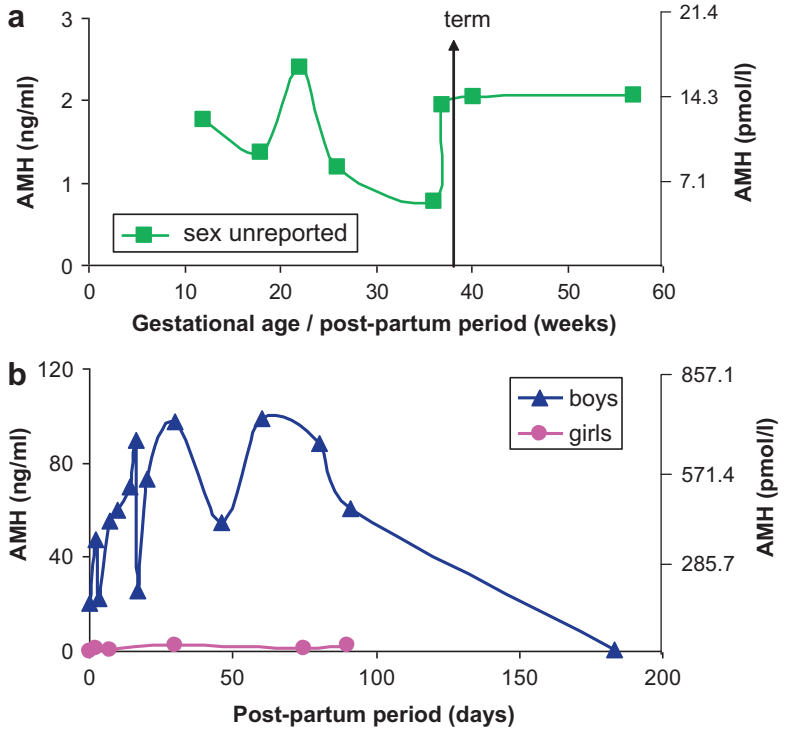

Figure 15 Weighted means of all reported maternal (**a**) and fetal and neonatal (**b**) serum AMH concentrations during gestation, at term and in the post-partum period. Data from Kuiri-Hanninen et al. (2011) are not included in (**B**) because these children were born preterm.

Rogers and Velten, 2011; Serin et al., 2001; Swerdlow et al., 1997; Trichopoulos, 1990; van de Beek et al., 2009). Moreover, markedly different circulating hormone concentrations were found among pregnant women from different ethnic backgrounds (Potischman et al., 2005) and in women that smoke compared with non-smokers (Speroff and Fritz, 2005). Some report higher oestrogen concentrations in multiparae compared with primiparae (Bernstein et al., 1986; Panagiotopoulou et al., 1990), in women under 30 years of age and in women carrying a female fetus (Speroff and Fritz, 2005).

Maternal samples

Overall, maternal serum oestrogens, inhibin A, SHBG, androstenedione and testosterone increase throughout pregnancy and reach their peak at birth. For most hormones, this is followed by a rapid decline in the post-par-

Table 22 Maternal serum AMH concentrations during gestation and post partum.

	Sex unreported		*Study*
	AMH (ng/ml)	n	
Gestational age (weeks)			
11—13	2.05	40	Li et al. (2010)
12	1.57	60	Nelson et al. (2010)
15—20	1.38	250	Li et al. (2010)
21—23	2.4	84	La Marca et al. (2005)
26	1.2	60	Nelson et al. (2010)
36	0.77	60	Nelson et al. (2010)
36—38	1.95	84	La Marca et al. (2005)
Post partum (days)			
1—2	2.05	84	La Marca et al. (2005)
120	2.07	60	Nelson et al. (2010)

AMH = anti-Müllerian hormone.

Table 23 Neonatal serum AMH concentrations.

Post partum (days)	*Girls*		*Boys*		*Study*
	AMH (ng/ml)	n	*AMH (ng/ml)*	n	
0			20.7	82	Aksglaede et al. (2010)
0	0.28	108			Hagen et al. (2010)
1—3			6.8	6	Lee et al. (1996)
1—30			25.2—154	9	Lahlou et al. (2004)
2	1.04	13	51.9	57	Bergada et al. (2006)
3			22.4	33	Lee et al. (1996)
4—30			26	29	Lee et al. (1996)
7			55.6	57	Bergada et al. (2006)
7	0.33	29			Kuiri-Hanninen et al. (2011)
7 (gestational age 35)	0.22	17			Kuiri-Hanninen et al. (2011)
7 (gestational age 31)	0.16	9			Kuiri-Hanninen et al. (2011)
10			59.8	57	Bergada et al. (2006)
14			69.9	57	Bergada et al. (2006)
20			73.2	57	Bergada et al. (2006)
30	2.55	13	97.9	57	Bergada et al. (2006)
30—90			36.4—162	10	Lahlou et al. (2004)
31—60			55	13	Lee et al. (1996)
60—90	1.28	21			Sir-Petermann et al. (2006)
61—120			60.9	21	Lee et al. (1996)
80			88.4	113	Pierik et al. (2009)
90	2.78	29			Kuiri-Hanninen et al. (2011)
90 (gestational age 35)	3.80	17			Kuiri-Hanninen et al. (2011)
90 (gestational age 31)	1.13	9			Kuiri-Hanninen et al. (2011)
1—365			0.66	53	Lee et al. (1996)

AMH = anti-Müllerian hormone.

tum period. For AMH and DHEAS, an inverse relationship is found, while gonadotrophin concentrations are negligible during gestation. Hormones were measured in other body fluids as well, for example amniotic fluid, urine or saliva. Concentrations in amniotic fluid (oestradiol, SHBG, androstenedione, DHEAS and testosterone) and saliva (oestrogens, testosterone) values are much lower compared with those measured in serum, except for amniotic fluid inhibin A and oestriol. Salivary steroid concentrations might be lower, because they reflect free steroids while in serum free and bound hormone concentrations are measured. Furthermore, salivary concentrations may differ because of salivary gland metabolism as well (Wood, 2009).

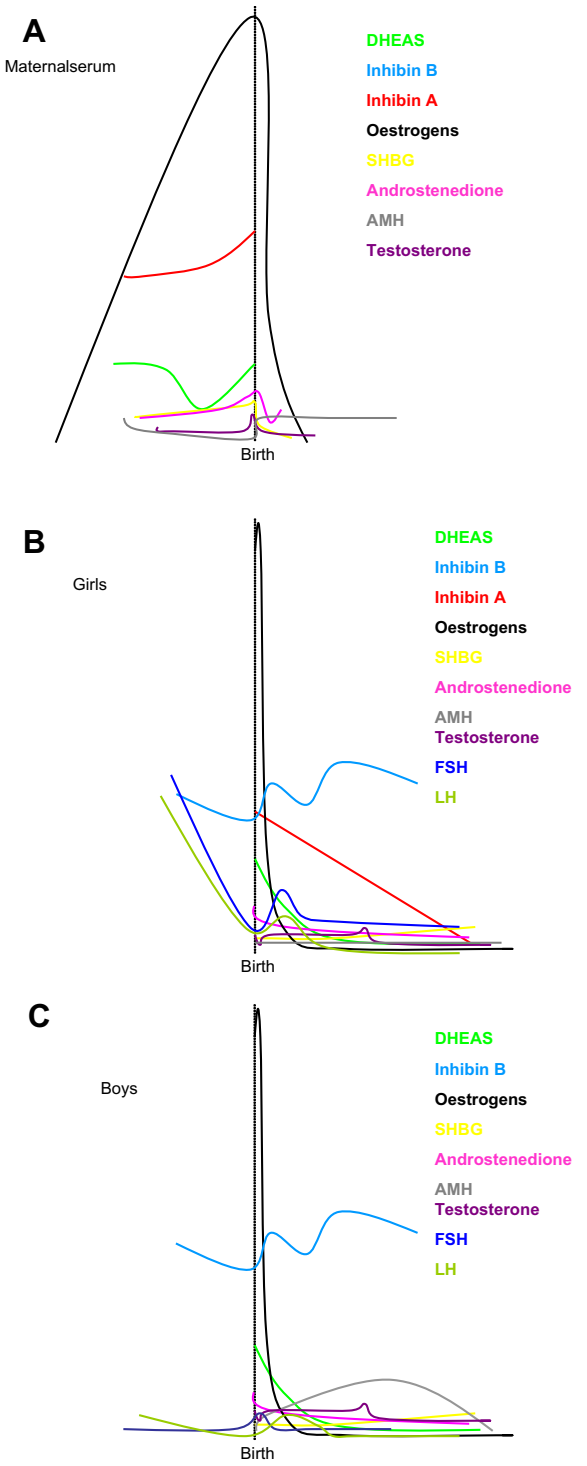

Figure 16 A global overview of endocrine changes during gestation and post partum in maternal serum (**A**), girls (**B**) and boys (**C**) during gestation, at term and in the post-partum period. Y-axis uses a logarithmic scale. AMH = anti-Müllerian hormone; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin.

Girls versus boys

Amniotic fluid oestradiol concentrations in mothers pregnant with a girl are higher compared with mothers carrying a boy, while maternal serum oestrogens showed no differences for fetal gender. For testosterone and androstenedione, this is the other way round: higher concentrations in amniotic fluid in mothers of boys and again no differences in maternal serum. Gonadotrophin concentrations taken from the umbilical cord at 24 weeks of gestation are much higher in girls compared with boys, while at term (gestational age 39 weeks) LH and FSH are very low irrespective of fetal gender (Debieve et al., 2000).

At birth, cord blood oestriol is significantly higher in females compared with males, while FSH is higher in cord blood from boys. For testosterone and DHEAS, there are studies reporting gender-related differences as well as papers that show no differences between the sexes.

During the post-natal period, boys have higher testosterone, inhibin B, LH and AMH concentrations, while girls have higher FSH concentrations. In boys, for FSH, LH and testosterone two distinguished peaks are shown, the first at about 1—2 months and the second at about 3—4 months (mini-puberty; Andersson et al., 1998). In order to interpret data obtained from children in whom defects in hypothalamic—pituitary—gonadal axis are suspected, one should take into account, that at about 1—2 months of age, there are physiological peaks in FSH, LH and testosterone concentrations.

Preterm versus term-born children

For premature births (gestational age 24—29 weeks), elevated LH and FSH concentrations in cord blood were demonstrated. Post partum, in girls an incredible increase in gonadotrophin concentrations in the first 2—3 months after birth was described. In boys this accounts for predominantly testosterone rise, but LH and FSH as well. This rebound effect might be explained by immaturity of the HPG axis or lack of adequate feedback on this system. For both preterm as well as term-born children, FSH and inhibin B demonstrate a mini-puberty at about 3—4 months of age, during which concentrations reach the highest pre-pubertal range (Bergada et al., 2002; Chellakooty et al., 2003; Ibanez et al., 2002). This is far less explicit for LH probably because of the short half-life and lack of data from birth to 3 months of age (Andersson et al., 1998). The supposed role for this hormonal surge involves endocrine alterations, imprinting of sexual orientation and behaviour and priming of target tissues for subsequent growth and maturation later in life. This suggests that hormones should be biologically active (Pierik et al., 2009; Raivio et al., 2003), which is confirmed by an increase in testicular volume following the hormonal rise (Kuijper et al., 2008) and faster penile growth in preterm boys (Kuiri-Hanninen et al., 2011). Overall, preterm-born children seem to develop some sort of catch up growth in terms of genital development, which follows raised steroid hormone concentrations.

Twins versus singletons

For twin pregnancies, substantial data are lacking. Significantly higher maternal serum oestradiol, oestriol, testosterone and urinary oestriol concentrations were reported in mothers of twins compared with singletons (Smith et al.,

Table 24 Hormone concentrations during twin gestation.

Origin of samples and hormone tested	*Study population*	*Hormone concentration*	*Study*
Maternal urine (24 h sample)			Gonzalez et al. (1989)
Oestriol (mg/24 h)	20—24 weeks (n = 16)	14.9	
	25—29 weeks (n = 21)	19.7	
	30—34 weeks (n = 44)	21.7	
	35—39 weeks (n = 24)	26.2	
Umbilical cord blood (96% >34.5 weeks)			Sakai et al. (1991)
Oestradiol (pg/ml)	Males		
	MZ (n = 46)	9150	
	DZ (same-sex) (n = 20)	10,330	
	Females		
	MZ (n = 26)	8150	
	DZ (same-sex) (n = 24)	10,110	
Testosterone (ng/ml)	Males		
	MZ (n = 46)	0.69	
	DZ (same-sex) (n = 20)	0.82	
	Females		
	MZ (n = 26)	0.55	
	DZ (same-sex) (n = 24)	0.58	
Maternal serum (26 weeks of gestation)			Smith et al. (2009)
Oestradiol (pg/ml)	Singletons	8961.6	
	Twins	12,421	
Oestriol (pg/ml)	Singletons	52,860.1	
	Twins	101,221.4	
Maternal serum (6—20 weeks of gestation)			Thomas et al. (1998)
Oestradiol (pg/ml)		4085.9	
Testosterone (ng/ml)		2.05	

DZ = dizygotic; MZ = monozygotic.

2009; Thomas et al., 1998). For twin neonates, higher testosterone concentrations were found in boys, but there are no differences in oestradiol for gender or zygosity in same-sex monozygotic or dizygotic twins. However, the studies reported here all have methodological problems. First and foremost, they have not taken into account the fact that twin samples can not be considered independent samples and therefore should not be analysed as such. Moreover, no (or insufficient) information is available on gestational age at sampling and birth, zygosity of the twins and ethnicity. Overall, the data are too broad to allow meaningful interpretation of these twin data.

Critical appraisal

In order to analyse information from all these different studies, this study has tried to summarize non-homogeneous information into interpretable graphical representations. This information contained means as well as median values, hormones measured by different techniques, in different units and often fetal gender was not reported. For example, for androgen measurement in adult women, radioimmunoassay and LC—MS show comparable outcomes (Janse et al., 2011). In cord blood and for neonates, however, it seems that androgens measured by LC—MS are lower compared with those measured by radioimmunoassay (Keelan et al., 2012). This might probably help explain why some articles reported conflicting data at comparable gestational ages or in the neonatal period.

This study has tried to report all available information as homogeneously as possible by converting data to the same unit and figures were constructed by using weighted means. The disadvantage of this method is that studies with a large number of subjects influence the data more compared with smaller studies, irrespective of any other study characteristics. However, this is the first review that combines information from different studies into graphical representations that help give an insight into hormone fluctuations during gestation and in the peri- and post-natal period. Strikingly, very limited data on twin pregnancies are available while, nowadays, a lot of research is based on supposed differences between twins and singletons.

Conclusions

Longitudinally measured endocrine data during gestation and in the peri- and post-natal period are lacking, especially for twin pregnancies. Maternal serum and amniotic fluid are used as a surrogate for fetal hormone exposure but this is probably not accurate.

Furthermore, using different measuring techniques, different units, different gestational ages of measurement

and the lack of information on fetal gender make it hard to interpret already existing data. This review has constructed graphical representationss for oestrogens, androgens, gonadotrophins, SHBG, inhibins and AMH to help give insight into fluctuations during gestation and post partum. Furthermore, when analysing hormone data, one should at least take into account fetal gender, gestational age, ethnicity, smoking, maternal age, body mass index and parity. A lot of work still has to be done to understand more about actual hormone concentrations during gestation, their biological activity and how they influence fetal development and their supposed effects later in life, especially in twins.

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 14 October 2012; refereed 28 February 2013; accepted 5 March 2013.