Anaesthesia during pregnancy

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Summary

Surgical procedures during pregnancy are mainly due to acute appendicitis or cholecystitis, and sometimes surgery for ovarian disorders and trauma will also be necessary. Anaesthetic and surgical management require a profound knowledge of the anatomical and physiological changes induced in pregnancy. Correction of hypovolaemia and hypotension and avoidance of maternal hypoxia and hypercarbia is essential for uteroplacental oxygen delivery and blood flow and thus for foetal health. Surgery should be performed at an experienced institution with neonatal and obstetric service. The main focus during anaesthesia is to maintain maternal and foetal vital functions and homeostasis, thus preserving the state of pregnancy. Intraoperative foetal monitoring should be applied if the foetus is viable, and an obstetrician should be available in case an emergency Caesarean section is necessary. None of the contemporary anaesthetic agents we use are known to have teratogenic potential. Nevertheless, exposures to any medication should be minimised, because adverse effects cannot be totally excluded. This is one of the reasons to favour regional anaesthesia, whenever possible.

Introduction

Surgical operations during pregnancy not indicated on account of obstetrical reasons are by no means seldom [1]; their rate ranges from 0.75% [2] to 2% [3] of all pregnant women, meaning that up to 14,000 surgical interventions for approx. 715,000 deliveries were made in pregnant women in Germany in 2014.

Among the surgical interventions with no elucidated causal connection to pregnancy, appendectomy ranks first with approx. 44%, followed by cholecystectomy with approx. 22% of cases [4]; other indications consist of ovarian pathologies (cysts, torsions, neoplasias), as well as trauma-related or oncosurgical interventions. However, the number of surgical interventions in pregnant women is higher, as about 2-4% of all childbearing women undergo surgery during an already existing, albeit yet undiscovered, pregnancy [5]. This also shows in the distribution of surgical interventions across the respective pregnancy stages: 42% of all interventions take place during the first trimester, 35% during the second trimester, and 23% during the third trimester [3,6]. In addition to the non-obstetrical indications for surgery, there are obstetrically indicated interventions which aim to avert impending premature delivery or miscarriage.

For all operations and the anaesthesias associated therewith, attention must be paid to several points simultaneously:

- Maintenance of homeostasis of both mother and developing child,

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- minimal negative effects on the further development of the foetus, especially prevention of foetal hypoxia or acidosis,
- no influence on the further course of pregnancy.

Knowledge of the pregnancy-induced physiological changes relevant to anaesthesia is indispensable to reach these goals.

Physiological changes during pregnancy which are relevant to anaesthesia

General considerations

Pregnancy produces distinctive, time-dependent changes affecting the entire organism of a pregnant woman. These physiological adaptation processes particularly involve the respiratory and cardiovascular system as well as the haematological-haemostasiological, gastrointestinal and renal system (Tab. 1). At the same time, hormone-induced tissue alterations of the integument, musculature and connective tissues (naturally also including the uterus) occur.

Respiratory system

In the course of pregnancy, alveolar ventilation is increased by way of both breathing rate (increase by 15%) and tidal air volume (increase by 40%) by up to 50%, whereas the functional residual capacity (FRC) decreases by about 20%.

This progesterone-mediated stimulation of the respiratory centre will be compensated at the end of pregnancy by an oxygen consumption increase of up to 20%. The arterial partial pressure of oxygen (paO_2) remains at first quite constant, then rises to a lesser extent until the date of delivery, whereas hyperventilation causes respiratory alkalosis with an arterial partial carbon dioxide pressure ($paCO_2$) decreasing up to 30 mm Hg and arterial pH values (despite compensatory bicarbonate reduction) exceeding 7.44 [7]. The decline of the FRC due to the pressure of the gravid uterus naturally increases in the course of pregnancy, and pregnant women's respiratory systems often struggle to tolerate a supine position. Altogether, these processes reduce apnoea tolerance, for which reason hypoxemia will emerge quickly in case of a rapid sequence induction (RSI).

The plethora of mucous membranes (typical during pregnancy) additionally reduces the diameter of the upper airways and might produce related intubation problems.

- The incidence rate of a difficult intubation is at 1:30; that of an impossible intubation at 1:280 – and is thus eight times more common than in non-pregnant patients [8].
- An age over 35 years, a body weight of >90 kg, a Mallampati score of >1 and absent labour were identified as risk factors for a difficult and/or impossible intubation [9,10].
- Furthermore, it was shown that the Mallampati score can deteriorate significantly not only in the course of pregnancy, but also during labour – and thus relatively acutely [11], so that a single evaluation, for example, at admission of the patient is not sufficient.

The intubation conditions must be always examined directly before the induction of general anaesthesia.

Cardiovascular system

Significant changes

During pregnancy the cardiovascular system adapts itself to the metabolic requirements of mother and foetus. Both the circulating blood volume and the cardiac output increase, whereas the peripheral resistance decreases.

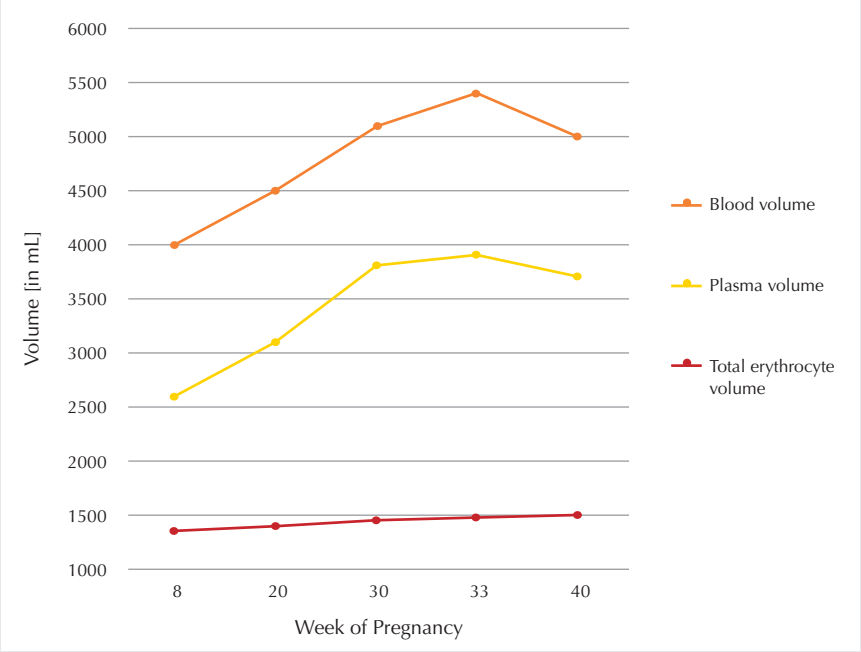
Blood volume

Starting with the eighth week of pregnancy, the circulating blood volume increases by up to 50 percent – reaching a culmination point in the 34th week of pregnancy (Fig. 1). As the percentage of red blood cells only increases by 20-35%, the overproportional increase in plasma

Tab. 1
Physiological changes in various organ systems in the course of pregnancy.

Organ system	Function	In third trimester
Respiratory system	Alveolar ventilation Oxygen consumption Functional residual capacity (FRC) Partial pressure of oxygen (paO_2) Partial pressure of oxygen of carbon dioxide ($paCO_2$)	↑ ↑ 50% ↑ 20% ↓ 20% ↑ to approx. 105 mm Hg ↓ to 32 mm Hg
Cardiovascular system	Heart rate Cardiac output Stroke volume Contractility Systemic vascular resistance	↑ 20% ↑ ↑ 50% ↑ 35% → ↓ ↓ 20%
Haematological-haemostasiological system	Erythrocyte volume Plasma volume Blood volume Platelets Fibrinogen, factor VII	↑ ↑ ↑ 50% ↑ ↑ 40% → ↓ ↑ ↑ 100%
Gastrointestinal system	Gastric evacuation Oesophageal occlusion pressure	→ ↓
Renal system	Glomerular filtration rate Renal plasma flow Osmolality	↑ ↑ 50% ↑ ↑ 50% ↓ 10%

Fig. 1



Physiological changes in various organ systems in the course of pregnancy.

volume results in a physiological anaemia of pregnancy, with a haemoglobin (Hb) value at about 11 g/dl.

The plasma volume displays particularly high increases between the 16th and 22nd weak of preganancy. At the same time, the distribution volume for drugs increases, and the concomitant hypoalbuminemia, associated with a reduced protein binding of certain drugs, might increase drug toxicity under certain circumstances.

Heart minute volume

The heart minute volume (cardiac output) increases by 50 percent in the course of pregnancy. While the increase in the first trimester primarily depends on the stroke volume (increase by about 35%), the further continuous increase until the 34th week of pregnancy results from an increase in the heart rate (10-15/min.). In addition, the reduced afterload contributes to an increase of the heart minute volume [12].

In total, the blood flow and oxygen supply exceed the consumption of oxygen distinctly, so that the uteroplacental unit is abundantly supplied with oxygen and nutrients.

After previous studies on the left-ventricular function failed to produce unequivocal results, more recent studies revealed that left-ventricular contractility decreases as pregnancy progresses and the end-diastolic and end-systolic volumes increase by the second trimester [13]. In addition, an eccentric hypertrophy with so-called left-ventricular remodelling appears in the further course of pregnancy [14].

The systemic and pulmonary vascular resistance decrease as early as in the first trimester, the underlying vasodilatory effects are mediated, for example, by relaxin, a peptide hormone of the corpus luteum [15]. Arterial compliance increases at the same time, whereas the response to vasoconstrictive drugs decreases. The combination of reduced peripheral vascular resistance and increased arterial compliance contributes to the maintenance of cardiovascular homeostasis through the action of the factors below [12]:

- Minimisation of diastolic blood-pressure decline,
- Reduction of left-ventricular pressure load,
- Limitation of endothelial shearing forces,
- Compensation of increased intravascular volume.

Despite the distinct decrease in peripheral resistance the arterial pressure decreases only a little – it is held nearly constant by an increase of the heart minute volume.

Cardiac arrhythmias

Arrhythmias during pregnancy, occurring as they do at a rate of 0.2-4%, are seldom and self-limiting in most cases without therapy.

The combination of haemodynamic, hormonal and vegetative-autonomous pregnancy changes are capable of both triggering pre-existing arrhythmias and inducing their initial manifestation. The increase of the blood volume appearing in association with an increased stretching of myocytes is considered to be the most important mechanism of pathogenicity [16]; this leads to an

- early afterdepolarization,
- shortened refractory period,
- prolonged transition, and
- spatial dispersion by means of stretch-activated ion channels.

Besides, re-entry phenomena frequently occur. The increased heart rate during the third trimester represents in itself an arrhythmogenic factor [17]. Furthermore, oestradiol and progesterone have been shown to display arrhythmogenic actions in laboratory animals [18], and oestrogen increases the number of adrenergic receptors in the myocardium.

After the exclusion of hyperthyroidism and life threatening diseases (e.g. pulmonary artery embolism, aortic dissection), arrhythmias should only be treated if they pose a threat to mother and foetus.

As systematic studies on the administration of antiarrhythmic agents during pregnancy do not exist, risks for the foetus cannot be ruled out categorically – among which are teratogenic effects (especially during organogenesis), decreased foetal growth and foetal arrhythmias (Tab. 2).

- In the event of **medication already pre-existing** for a longer period, the administration of antiarrhythmic substances with a low foetal risk should be continued, as in this case the stability of the female patient outweighs the potential risks for the foetus [16].
- If new **supraventricular extrasystoles** appear treatment with β_1-blocking agents may proceed at best after completion of the first trimester.
- **Supraventricular tachycardias** (SVT) are the most common arrhythmias occurring during pregnancy, and about 20% of the female patients with pre-existing SVT increasingly display symptoms in the course of gravidity. These symptoms mostly consist of AV node re-entry tachycardias (AVNRT); if vagal manoeuvres are ineffectual they can be reliably treated with adenosine.
- **Ventricular tachycardias** and **ventricular fibrillation** are very seldom and mostly have a structural cause (cardiomyopathy, coronary dissection, coronary spasm). Ventricular arrhythmia can be terminated with ajmaline; amiodarone should not be administered because of its teratogenic actions [19]. In case of haemodynamic instability an **electrical cardioversion** will be indicated; an induction of foetal arrhythmias is of rare occurrence, and the uteroplacental blood flow will not be compromised [20]. If pregnancy is in an advanced stage, an induction of labour has been described, also foetal arrhythmias which demanded an emergency section [21]. For these reasons, monitoring of the foetal heart rate in the already viable foetus is recommended in this situation – also for **electrophysiological examinations** and a catheter ablation.

Tab. 2
Undesired effects and teratogenicity of antiarrhythmic drugs during pregnancy and lactation. Modified after [16].

Substance	Potentially undesired effects	Teratogenicity	Lactation
Quinidine	Thrombocytopenia, ototoxicity, Torsade de pointes	no	possible to a limited extent
Lidocaine	Bradycardia, undesired CNS effects	no	possible
Flecainide	Good tolerance unless a structural heart disease exists	no	possible
Propafenone	Good tolerance unless a structural heart disease exists	no	unknown
Propranolol	Bradycardia, growth retardation, postpartum apnoea in the newborn	no	possible
Metoprolol	Bradycardia, growth retardation, postpartum apnoea in the newborn	no	possible
Atenolol	Bradycardia, growth retardation, postpartum apnoea in the newborn	no	no
Amiodarone	Foetal hypothyroidism, growth retardation, premature delivery	yes	avoid
Dronedarone	Malformation of vessels and limbs, cheilognathopalatoschisis	yes	contraindicated
Verapamil	Maternal hypotension, foetal bradycardia	no	possible
Diltiazem	Maternal hypotension, foetal bradycardia	unknown	possible
Adenosine	Dyspnoea, bradycardia	no	unknown
Digoxin	Lowered birth weight	no	possible

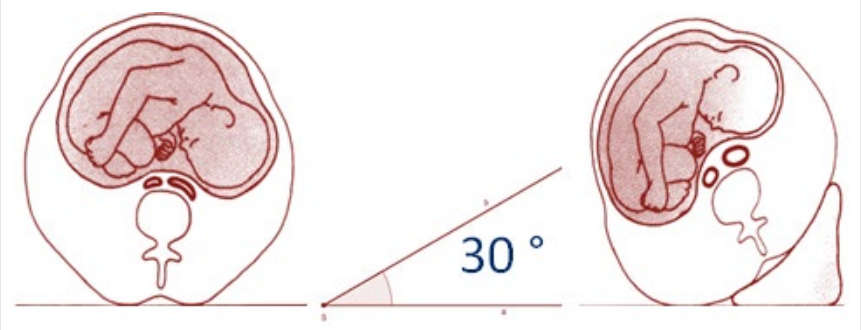
Vena cava compressions syndrome (supine hypotension syndrome)

In pregnancy, the enlarged uterus impedes with the venous backflow from the legs and pelvis by an immediate compression of the inferior vena cava and by an increase of intraabdominal pressure.

In supine non-pregnant women, the pressure in the inferior vena cava amounts to 4-7 mm Hg; it will increase to 20-30 mm Hg in late pregnancy. The compression of the inferior vena cava, however, might already assume haemodynamic relevance by the 16th week of pregnancy and reduce the heart minute volume by 25-30%. The symptoms range from unspecific complaints to cardiovascular arrest with life-threatening consequences for mother and child. Neuroaxial anaesthesia procedures with supine positioning often lead to arterial hypotension after the 20th week of pregnancy. Left-lateral tilt positioning is recommended as a prophylaxis for pregnant women [22], as it reduces the pressure in the inferior vena cava to 10-15 mm Hg. Magnetic resonance imaging (MRI) [23] revealed that only a left-lateral position of about 30 degrees was able to restore the original diameter of the inferior vena cava (Fig. 2). A relevant compression of the abdominal aorta, however, could not be confirmed by MR imaging [23], for which reason the term "aortocaval compression syndrome" will be avoided here.

Wake pregnant women must be monitored not only with regard to haemodynamics (blood pressure,

Fig. 2



30° left lateral tilt position to relieve the inferior vena cava – the inferior vena cava is free of compression only after a 30-degree angle is reached.

heart rate), but also for clinical symptoms. A feeling of sickness, nausea and perhaps vomiting are important symptoms, to which an immediate response should proceed by bringing the patient in a 30 degrees left-lateral tilt position [24].

Haematological-haemostasiological system

The coagulation equilibrium shifts toward coagulation during pregnancy. The procoagulant state reduces the maternal blood loss at childbirth, but it is also accompanied by an increased incidence (1:1.000-1:2.000) of thromboembolism [25].

In a normal pregnancy, the concentrations of the coagulation factors I (fibrinogen) and VII as well as factors VIII, IX and the von-Willebrand's factor (vWF) increase, whereas the concentration of factor II (prothrombin) rises only moderately (Tab. 3). Among the anti-coagulative factors, protein C and antithrombin mostly remain unaltered, whereas protein S is often markedly decreased. Fibrinolytic activity during pregnancy and peripartum is reduced due to an increased activity of the plasminogen activator inhibitor from endothelium cells and the placenta. The values of the coagulation factors return to normal at about 4-6 weeks after childbirth, whereas protein S might remain reduced for some time longer. In addition, 5-8% of all pregnant women have a gestational thrombocytopenia with an increased platelet turnover [26], which is based on pregnancy-induced haemodilution. This condition disappears after delivery.

Tab. 3

Coagulation factors during pregnancy. Mod. after [27, 28]. **vWF** = von-Willebrand's factor.

Coagulation factor	Change
Prothrombin (II)	(↑)
Fibrinogen (I), VII	↑ ↑
VIII, IX, vWF	↑
X, XI, XII	→
Protein S	↓ ↓
Antithrombin (AT), protein C	→
Plasminogen	↑
D-dimers	↑

Tab. 4

Reference ranges for rotation thromboelastography/-metry (ROTEM). After [29].

Test	CT [s]	CFT [s]	MCF [mm]
EXTEM	31-63	41-420	42-78
INTEM	109-125	40-103	63-78
FIBTEM	31-79		13-45
APTEM	33-62	42-118	61-79

CT = clotting time;
CFT = clot formation time;
MCF = maximum clot firmness.

Tests:
EXTEM = extrinsic system (equivalent to Quick's test);
INTEM = intrinsic system (equivalent to aPTT; activated partial thromboplastin time);
FIBTEM = fibrinogen percentage of the clot;
APTEM = hyperfibrinolysis.

The increasing availability of point-of-care methods in coagulation diagnostics has inspired a research group in the Netherlands [29] to compile peripartal reference ranges applicable to rotation thromboelastography/-metry (Tab. 4).

Gastrointestinal system

Gastric evacuation is not invariably delayed during pregnancy [30], but 30-50% of pregnant women do have a gastroesophageal reflux. However, the increasing intraabdominal pressure during pregnancy– supported by a reduced oesophageal occlusion pressure – increases the risk of aspiration.

Pregnant women after the 20th week of pregnancy – and until 24 h postpartum – are considered as patients who pose a high risk of regurgitation and pulmonary aspiration of stomach content – for this reason a rapid sequence induction (RSI) is categorically necessary [31].

Besides, an anatomical displacement of the cecum by the gravid uterus is being discussed as the cause for the increased incidence of appendicitis during pregnancy [32].

Renal system

Pregnancy has considerable effects on osmotic regulation, volume homeostasis and the urinary excretion system. The kidney volume increases as early as in the first trimester and rises in the third trimester – with concomitant renal vasodilatation and hyperfiltration – to about 150% of the initial value. Progesterone and its metabolites, relaxin, prostaglandins and nitrogen monoxide (NO) have an enhancing effect on the renal plasma flow and glomerular filtration rate; glycosuria is not of seldom occurrence, proteinuria may also appear occasionally. Owing to reduced concentrations of sodium and urea, plasma osmolality

decreases by 8-10 mosmol/kg – a condition which would immediately result in a pronounced water diuresis in non-pregnant women, whereas in pregnant women a new equilibrium arises due to changed threshold limits for the antidiuretic hormone (ADH) and thirst. The superior segments of the ureters are often dilated, without the existence of any pathological obstruction [33].

Foetal safety

Teratogenicity and other drug-related actions

General aspects

Most reports of teratogenicity and other actions of medicinal drugs during pregnancy are based on in-vitro and animal studies or on a retrospective evaluation of drug exposures – e.g. the active substance thalidomide in the so-called Contergan scandal.

Organogenesis in the first trimester is an especially vulnerable stage of pregnancy.

- During the first 15 days of gestation, drugs mostly elicit an all-or-nothing effect: the foetus remains fully intact or is lethally damaged.
- Subsequent to this first and highly vulnerable stage, drugs are capable of influencing organogenesis up to the 65th day of gestation; potential consequences are generalised embryotoxicity, malformation syndromes as well as manifold and sometimes subtle morphological, biochemical and functional disorders [34].

In total, about 15% of all known pregnancies end with an abortion; the risk is highest in the first trimester, with a rate of about 80 % of all abortions. In this context, an overview of data derived from 12,452 pregnant women has shown that the incidence rate of abortions in case of non-obstetrical interventions in the first trimester amounted to 10.5% [35] – and thus lies within the same range that applies to pregnant women who did not undergo surgery.

The **incidence of a medication** during pregnancy has several aspects. Many women take at least one drug; taking four or more products has more than doubled in the last 30 years [36]. While numerous pregnant women suffer from chronic diseases like bronchial asthma, hypertension or diabetes mellitus, which require medication during pregnancy as well, new diseases or the exacerbation of a pre-existing condition may also require drug therapy. In addition, pregnancy–related alterations occasionally also make dose adjustments necessary.

The five-tiered **risk assessment** (classes A, B, C, D, X) applicable to drugs taken during pregnancy and established since 1979 by US Food and Drug Administration (FDA) was abandoned on June 30, 2015. Since that time, the risks for pregnancy and lactation are registered collectively in the "Pregnancy and Lactation Labelling (Drugs) Final Rule" [37]; together with the discussion of the underlying data, it is supposed to provide relevant information for decision-making either for or against the use of a substance and for counselling pregnant and lactating women. Furthermore, the Centre for Pharmacovigilance and Advocacy (Berliner Pharmakovigilanz- und Beratungszentrum (PVZ) for Embryonal Toxicology in Berlin (a publicly funded independent institute) informs about the tolerance of important drugs and the treatment of diseases frequently occurring maternal during pregnancy and lactation on its website (**www.embryotox.de**).

Special actions of anaesthetics

As yet, both experiments conducted with animals and observational studies on pregnant women failed to reveal an unequivocal teratogenic effect of any substance relevant to anaesthesia (Tab. 5).

Anaesthetics are capable of affecting cell differentiation and organogenesis by numerous modes of action (intracellular signal transduction, effects on mitosis and DNA synthesis) [6]. Outside the especially vulnerable stage of organogenesis (first 15-65 days of gestation), however, almost all anaesthetics and analgesics are considered to be safe, although special safety studies with pregnant women do not exist for reasons which are quite obvious.

Selection of the anaesthetics should be guided by the available literature and specific pharmacology; preference should be given to tested and established substances.

Pertinent data are available on the internet platform http://www.embryotox.de. During obtaining informed consent, reference should be made to the potential off-label use of a drug and, if possible, the drugs planned to be used should be explicitly listed.

- Data derived from a Swedish Register [3] confirm a slight increase of premature deliveries after interventions during pregnancy – it cannot be said whether this has been effected by the respective intervention, the underlying pathology or the applied anaesthetics. After interventions into the pelvis and abdomen because of adnexal pathologies and appendicitis in the third trimester, premature labour was increasingly observed (without an increased risk of miscarriages) [38].
- An increased incidence of neural tube defects has been correlated with an inhibition of methionine synthesis due to the oxidation of vitamin B_{12}. As **dinitrogen monoxide (N_2O; laughing gas)** oxidises vitamin B_{12} and teratogenic and abortive effects have been described after the application of very high concentrations in experiments with animals, N_2O should not be applied, according to the present state of knowledge, during the highly vulnerable stage of organogenesis (first 15-65 days of gestation).
- The administration of **diazepam** was seen to be correlated with an increased rate of orofacial clefts, intestinal atresia, cardiac malformations and pylorus stenosis. Although

Tab. 5
Potential foetal and neonatal risks of medicinal drugs with relevance to anaesthesiology.

Substance group	Substance	Potentially undesired actions against the foetus/newborn	Teratogenicity	Lactation period
Opioids	Sufentanil, fentanyl, remifentanil, morphine	Crosses the placenta, respiratory depression, withdrawal syndrome possible in case of long-term therapy	Not known	No limitation if applied in normal doses, attention in case of apnoea tendency
Hypnotics	Propofol	Cross the placenta, higher doses cause respiratory depression	Not known	No limitation
	Thiopental	Cross the placenta, respiratory depression	Not known	No limitation
	Etomidate	Decreased cortisol concentration	Not known	No limitation
	Midazolam	Crosses the placenta, respiratory depression, muscular hypotension	Probably safely applicable	No limitation
	Ketamine	Cross the placenta (increases uterus tonus in first and second trimester)	Not known	No limitation
Inhalation anaesthetics	Sevoflurane	Higher doses cause respiratory depression	Not known	No limitation
	N_2O	Inhibition of methionine synthesis by oxidation of vitamin B_{12}	In the first trimester perhaps neural tube defects	No limitation
Gluco-corticoids	Dexamethasone	Intrauterine growth retardation, premature birth, hypoglycaemia, hypotension and electrolyte disorders	Slightly elevated risk for cleft palates cannot be ruled out	No documented information
Neuromuscular blocking agents		Cross the placenta poorly	Not known	No limitation
Sympatho-mimetic agents, vasocon-strictors	Theodrenaline/ cafedrine	Decreased uteroplacental perfusion	Not known	No limitation
	Ephedrine	Decreased uteroplacental perfusion	Not safe: In the first trimester perhaps association with gastroschisis, duodenal atresia, hemifacial microsomia, ventricle septum defect	No limitation
	Phenylephrine	Decreased uteroplacental perfusion	Not known	No limitation
	Adrenalin	Decreased uteroplacental perfusion	Not known	No limitation
Antihyper-tensive drugs	α-Methyldopa	Cross the placenta, no undesired effects, antihypertensive of first choice during pregnancy	Not known	No limitation
	Dihydralazine	Crosses the placenta, seldom hepatotoxic-ity and "pseudo lupus"	Not known	No limitation
	Clonidine	Crosses the placenta, elevated blood pressure	Not known	Better do without: Neonates display up to 66% of maternal plasma levels
	ACE inhibitors	Crosses the placenta	1st trimester: malformations of the cardiovascular system and the CNS; 2nd and 3rd trimester: decreased uteroplacental perfusion, hypotension, anuria, skull hypoplasia, joint contractures, pulmonary hypoplasia	No consequences yet observed
	Metoprolol	In case of permanent therapy possible reduction of placental weight and birth weight	None known	Single cases of bradycardia
Antiemetic drugs	Odansetron	Lacking data, should only be applied in case of failure of better examined antiemetics and severe symptoms	Not unknown	Should be applied in case of failure of better examined antiemetics only
	Dimenhydrinate	Should be avoided in the 3rd trimester because of its potential contractility-stimulating effects on the uterus	Comprehensive studies, no teratogenic effects known	Antihistaminic drug effects: sedation or hyperexcitability

no clear evidence exists, it is recommended to do without benzodiazepines in the first trimester.
- In addition, it is being discussed whether epidemiological data, and data derived from experimental studies with animals, focusing on the exposure of foetuses with general anaesthetics, are capable of explaining neurocognitive deficiencies. A final assessment of this subject is not possible yet [39].

Prevention of intrauterine foetal asphyxia

The greatest anaesthesiological challenge is to prevent foetal asphyxia.

As the uteroplacental unit does not possess autoregulation, sufficient perfusion primarily depends on the maternal perfusion pressure and the cardiac output as well as the oxygenation and the $paCO_2$ of the expectant mother.
- Although a short-term **maternal hypoxemia** is tolerated by the foetus, a prolonged maternal oxygen deficiency results in uteroplacental vasoconstriction and subsequently in foetal hypoxemia, acidosis and death.
- **Maternal hypercapnia** affects the diffusion of CO_2 from the foetal to the maternal circulatory system and induces foetal acidosis.
- Pronounced **maternal hypocapnia** can also induce foetal acidosis by means of direct uteroplacental vasoconstriction [6].

Practical procedure

Time-dependent prioritisation

Emergency interventions must proceed immediately, whereas elective interventions should be categorically postponed until after delivery.

Even if no indications of an increased risk of abortion or teratogenicity due to anaesthetics applied in the first trimester exist, a causal relationship to surgical and/or anaesthesiological therapy will perhaps be seen whenever an undesired event (abortion, vaginal haemorrhage, foetal malformation) occurs, so that any surgical intervention during organogenesis will require a strict indication. Urgent interventions, for example, in cases of acute appendicitis or cholecystitis, however, should never be delayed because of concerns over potential teratogenicity. Interventions which are not urgent, but cannot be postponed until after childbirth, should proceed, whenever possible, in the second trimester [40], because teratogenic effects, preterm delivery and/or induction of labour will have the lowest risk in this period.

Preoperative evaluation

No additional examinations will be necessary in case of an uncomplicated pregnancy; the preoperative evaluation is the same as for non-pregnant patients.

After perusal of the Expectant Mother's Record of Prenatal and Natal Care, a focused medical case history should proceed concerning special internal medical and obstetrical circumstances – pre-eclampsia, pregnancy-associated hypertension, HELLP syndrome (haemolysis, elevated liver enzyme levels, low platelet count; haemolytic anaemia, increased liver parameters, thrombocytopenia) and gestation diabetes as well as a precise evaluation of the airway in particular.

General preparation of patients

In matters of patient preparation, especially the elevated risks of aspiration and thromboembolism as well as the increased incidence of difficult intubation have to be observed.

- Combining an antacid agent with an H2 blocker is most effective in order to **raise the pH of the gastric juice** in the third trimester [41].
- An either pharmacological or mechanical **thrombosis prophylaxis** should proceed depending on the duration of the surgical intervention [42].
- The **intubation conditions** must be checked again carefully immediately before onset of the surgical intervention.
- A perhaps necessary perioperative **antibiotic prophylaxis** can be done by applying penicillins, cephalosporins, erythromycin and clindamycin, whereas tetracyclines, fluoroquinolones and sulphonamides are considered as second-choice antibiotics.
- Although intraoperative manipulations of the uterus can induce labour, the prophylactic administration of tocolytic drugs is not indicated [43].

To avoid a vena cava compression syndrome a supine position starting in the 16th to 20th week of pregnancy should only be done in combination with a 30 degree left lateral position.

Foetal monitoring

Type and extent of foetal monitoring depend on the stage of development.

In a **potentially viable foetus** (approximately from the 23rd week of pregnancy onward) the heart rate and thus the perfusion of the uterus should be issues of perioperative monitoring and documentation; beyond this, labour activities should perhaps be registered by cardiotocography (CTG) before and after surgical intervention. With regard to potential indications for surgical delivery of the foetus, an intraoperative monitoring of the foetal heart rate will be recommended especially for positioning, ventilation and cardiovascular therapy of the expectant mother, whereby the interpretation requires a qualified professional. A Doppler ultrasound measurement of the foetal blood flows (transcutaneous or transvaginal)

may provide additional information. In the event of a disordered uterus perfusion an intervention will have to proceed without delay, for example, by correcting a state of hypoxia, increasing the blood pressure, or correcting the positioning. However, a "silent" oscillation pattern of the CTG with a small bandwidth is not considered as pathological – as opposed to the usual evaluation – under the supply of volatile or intravenous anaesthetics [44].

In a **potentially not yet viable foetus** measuring the heart rate by Doppler sonography before and after the intervention will be sufficient.

Anaesthesia

General aspects

The anaesthesiological procedure depends on

- the type of surgical intervention,
- the effects of the anaesthetics and the intervention on female patient and foetus, and
- the physiological changes due to pregnancy

There is no evidence showing that maternal **general or regional anaesthesia** produce different actions in the foetus. However, theoretical considerations with regard to pregnant woman (endotracheal intubation, aspiration) and the foetus (acidosis, teratogenicity) speak in favour of regional anaesthesia in general – although the most common operations during pregnancy are abdominal operations and thus regularly require general anaesthesia.

Propofol, fentanyl and midazolam are commonly used for **analgosedation**. In this case, it must be observed that maternal hypoventilation with consecutive acidosis will have serious consequences for uteroplacental perfusion and the foetus. In addition, there is an increased risk of aspiration in case of deep sedation during the late stages of pregnancy, for which reason, general anaesthesia with rapid sequence induction (RSI) will be recommended in cases of hyperemesis gravidarum vomiting and after the 20th week of pregnancy.

Induction and maintenance of general anaesthesia

The induction of anaesthesia after the 20th week of pregnancy will mostly be carried out – after careful pre-oxygenation – by rapid sequence induction (RSI).

Whether this is really necessary is under discussion [45] – the incidence rate of aspiration is very low in pregnant women and there are no data that demonstrate the superiority of the rapid sequence induction (RSI).

- Thiopental and propofol can be used as induction hypnotics.
- According to previous findings, ketamine (and/or analogous esketamine) is capable of increasing the uterus tonus and causing foetal asphyxia [46] and should be avoided in the first and second trimester. This action cannot be confirmed in the third trimester.
- After the administration of etomidate the plasma concentration of cortisol is not only decreased in the mother, but also in the newborn [47].
- Neuromuscular blocking agents do not pass the placental barrier. A lower activity of plasma cholinesterase toward the end of pregnancy is the reason for prolonged effects of succinylcholine [48,49].
- Starting as early as in the 8th week of pregnancy, the minimum alveolar concentration (MAC value) of volatile anaesthetics will be reduced by about 30% in pregnant women as compared to non-pregnant women [50].

With respect to the physiological respiratory alkalosis of the pregnant woman, ventilation during anaesthesia should be adjusted to an end-tidal CO_2 value of approx. 30 mm Hg.

An even more pronounced hypocapnia must be avoided, because it will reduce the perfusion of the uteroplacental unit – just like a hypercapnic state would – and lead to foetal acidosis. Furthermore an inspiratory oxygen fraction (FiO_2) of 0.5 is recommended categorically [51].

Cardiovascular management

Every form of general or regional anaesthesia and analgosedation require frequent measurements of maternal cardiovascular functions (ECG, pulse oximetry, either oscillometric or invasive blood-pressure measurements) and, if necessary, immediate intervention.

In case of maternal hypotension, apart from the prioritised volume therapy, a vasoconstriction by administration of phenylephrine will be possible – without a negative impact on the foetus [52,53]; however, a critical reduction of the heart minute volume due to an increased afterload must be avoided. Theoadrenaline/cafedrine (Akrinor) produce a longer lasting blood-pressure increase by means of a predominant stimulation of β1 receptors and to a lesser extent of α receptors as well.

Postoperative analgesia

In general, only few special features must be observed in postoperative analgesia.

- Opioids can be administered, however, special attention must be given to the prevention of an opioid-induced hypoventilation in pregnant women.
- Beginning with the 32rd week of pregnancy, paracetamol is the non-opioid analgesic of choice in case of slight and moderate pain.
- Epidural anaesthesia has advantages after larger surgical interventions into the chest, abdomen and lower limbs.
- Nonsteroidal anti-inflammatory drugs (NSAID) should not be administered, especially after the 32rd week of pregnancy, as they might induce the premature occlusion of Botallo's duct in the foetus by inhibition of prostaglandin synthesis [54].

Postoperative maternal morbidity

A retrospective analysis [55] of numerous pregnant and non-pregnant patients who had to undergo appendectomy or cholecystectomy failed to reveal the increased maternal morbidity of those who were pregnant. A US-American cohort study [56] which included over 7,000 pregnant women with acute appendicitis, however, revealed that their risk of peritonitis was 30 percent higher in pregnant women than in non-pregnant women; pregnant women also had a 50 percent higher incidence rate of sepsis, septic shock, transfusion, pneumonia, ileus and postoperative wound infection. Furthermore, their risk of septic shock, peritonitis and thromboembolism was markedly higher when non-surgical instead of surgical interventions had been applied.

Special surgical aspects

Laparoscopic interventions

Laparotomy used to be the sole option in cases of abdominal surgery. Today pregnant women increasingly undergo laparoscopic surgery – in the USA [57] they make up 64.8% of all intraabdominal interventions (appendectomy, cholecystectomy, etc.).

- Laparoscopic appendectomies revealed an increased rate of miscarriages in several case series [58, 59,60], for which reason the open surgical procedure must be recommended in case of an appendicitis [61].
- Laparoscopic cholecystectomy, however, is considered as the method of choice for pregnant women – regardless of the week of gestation. A nonsurgical therapy regularly leads to relapses. In addition, the morbidity and mortality of the patients is increased. While laparoscopy is in progress (Tab. 6), a pneumoperitoneal pressure of up to 16 mm Hg is recommended – apart from other measures – in order to avoid excessively high cardiovascular stress on the pregnant woman with reduced uteroplacental perfusion and too high an increase in maternal paCO2 levels (each harbouring the risk of foetal acidosis) [61]. In case of pre-existing maternal gas-exchange disorders, arterial blood-gas analyses are only recommended to monitor the $paCO_2$ [1].

Tab. 6
Recommendations for the laparoscopy of pregnant women [6].

- Open technique for laparoscopic access
- Maternal end-tidal $paCO_2$ 30 - 35 mm Hg to avoid foetal acidosis
- Limited pneumoperitoneal pressure (11-16 mbar) or gas-free method
- No extreme positioning, gradual position changes
- Monitoring of foetal heart rate and uterus tonus

Tab. 7 gives an overview of the indications and special circumstances of laparoscopic interventions [61].

Tab. 7
Indications for surgery and special circumstances of laparoscopic operations during pregnancy. After [61].

Indication	Special features
Acute appendicitis	Increased frequency of abortion in case of laparoscopic surgery
Cholelithiasis, cholecystitis	Laparoscopic cholecystectomy does not depend on length of pregnancy, method of choice Nonsurgical therapy is significantly more often correlated with problems
Adnexal torsion, adnexal tumour	Symptomatic adnexal findings should be diagnosed by laparoscopy in order to prevent the loss of an organ
Symptomatic myomas	Enucleation during pregnancy (only 2.1% require therapy) is mostly done by performance of open surgery Case studies about successful laparoscopic enucleations
Symptomatic ovarian cyst	Randomised controlled studies on the optimal access do not exist

Procedures in cases of trauma

Nearly every twelfth pregnant woman (8.3%) suffers a trauma during her pregnancy, sometimes with serious consequences for maternal and foetal morbidity and mortality [62].

As a rule, the life of the mother has the highest priority, for which reason stabilisation of the mother must proceed before evaluation of the foetus. This includes all necessary drug treatments or invasive measures including radiological diagnostics – irrespective of the status of the foetus or its potential risk.

As yet, no explicit teratogenic effect could be evidenced at a **radiation exposure** of <100 mGy (10 rd). The highest radiation risk (with growth retardation, microcephalus or mental retardation) exists during the 8th to 15th week of pregnancy; the risk is low after the 26th week of pregnancy. The ACOG (American Congress of Obstetricians and Gynecologists) recommends a maximum dose of approx. 50 mGy (5 rd) for the foetus; no increased risk of foetal anomalies or abortions is associated with this dose [63]. In case of a heavy trauma the risk of foetal radiation exposure is negligible compared to the risk of insufficient diagnostics – and therefore to be disregarded altogether. Tab. 8 shows the radiation dose absorbed by the foetus during selected radiological examinations.

The sensitivity and specificity of **trauma sonography** (FAST; Focused Assessment with Sonography for Trauma) is nearly identical in pregnant and non-pregnant women. A traumatic detachment of the placenta, which mostly occurs after the 16th week of pregnancy and is associated with a high foetal mortality rate, will be discovered in only 25-57% of the cases [64,65].

When treating pregnant women, it must be observed that foetal hypoxia might even appear when the maternal cardiovascular parameters are normal.

Tab. 8
Radiation dose absorbed by the foetus according to data reported by the ACOG [63].

Examination	Radiation dose absorbed by the foetus (mGy)
Cervical spine (a.p., lateral)	<0,001
Limbs	<0,001
Thorax (p.a., lateral	0,002
Thoracic spine (a.p., lateral)	0,003
Abdomen (a.p.)	1 - 3
Lumbar spine (a.p., lateral)	1
CT skull	0
CT of the thorax	0,2
CT-angiography of pulmonary artery	0,2
CT of abdomen	4
CT of abdomen and pelvis	25
Foetal background dose during 9 months of pregnancy	0,5 - 1
General recommendation of the ACOG	<50

ACOG = American Congress of Obstetricians and Gynecologists; **a.p.** = anterior-posterior; **CT** = computer tomography.

An impairment of uteroplacental perfusion develops prior to the clinical signs of maternal shock – the risk of impaired foetal perfusion must therefore always be observed in case of pregnant trauma patients.

If a pregnant woman has to undergo resuscitation consequential to a suffered trauma – or for other reasons – a perimortem section must be taken into consideration.

There are several case reports of a favourable maternal and foetal outcome [66]. The European Resuscitation Council (ERC) recommends an emergency caesarean section to rescue a child viable according to the pregnancy status after four minutes of futile resuscitation and substantiates this finding with pertinent data [67].

Summary of recommendations

There are no major randomised studies focusing on the anaesthesia of pregnant women, for which reason pertinent recommendations [40,51] rely on observational studies, expert opinions and the exploration of caesarean section studies. However, the following key points can be regarded as corroborated to a greater extent:

- The physiological changes during pregnancy require adjustments of anaesthesiological and surgical procedure.
- Emergency interventions must proceed immediately, whereas elective interventions should be generally postponed until after delivery. Interventions without urgency, which cannot be postponed to a point in time after delivery, should be carried out in the second trimester.
- None of the currently used anaesthetic agents unequivocally elicits teratogenic actions. However, as undesired effects cannot be ruled out with absolute certainty, exposure must be kept at a minimum.
- Treatment should take pace in a facility which has interdisciplinary experience with the surgical therapy of pregnancy women (with obstetrical and neonatological expertise). An obstetrician should be available to carry out a caesarean section directly.
- The increased risk of thromboembolism in pregnant women requires a thrombosis prophylaxis.
- In case of a not yet viable foetus, an evaluation of the foetus's heart rate by Doppler sonography before and after intervention will be sufficient. If the foetus is viable, the foetal heart rate and perhaps the maternal labour activity should be recorded by CGT at least before and after the intervention. As far as potential indications for surgical delivery of the foetus are concerned, an intraoperative monitoring of foetal heart rate is recommended, especially during positioning, ventilation and cardiovascular therapy of the expectant mother; the interpretation of the foetus's heart rate will require a qualified professional.
- Pregnant women are considered as not fasting after the 20th week of pregnancy, for this reason a rapid sequence induction (RSI) is categorially required.
- The left lateral position reduces the risk of vena cava compression syndrome.
- A regional anaesthesia reduces pregnant women's exposure to drugs and the necessity of airway management.
- Maternal hypotension, hypoxemia, hypercapnia and hypocapnia must be avoided in order to maintain foetal homeostasis. A FiO_2 of 0.5 and an end-tidal pCO_2 of about 30 mm Hg is recommended.
- The gravid uterus should be manipulated as little as possible.

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